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DISPOSABLE MEMBRANE OXYGENATOR (HEART-LUNG MACHINE) AND ITS USE IN EXPERIMENTAL SURGERY

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PROLONGED OPERATIONS in the open heart at normal body temperature require heart-lung machines as a substitute for cardiopulmonary function. The principle of all these is the same: they withdraw blood from the venae cavae, oxygenate it, and return it into the aorta. Thus the patient's heart is completely bypassed (Fig. 1). It was believed for a long time that the machine would have to pump and oxygenate blood in amounts equal to the normal resting cardiac output—at least 100 ml. per kg. of body weight per minute. Accordingly, several elaborate machines have been devised to pump and oxygenate 5 liters of blood per minute, for example by Dennis,[1] Jongbloed,[2] and Kolff and Dubbelman.[3,4] The most successful design was that of Miller, Gibbon, and Gibbon.[5] A similar machine is in use at the Mayo Clinic[6,7] with outstanding success; its complexity and cost have prevented its wider use.

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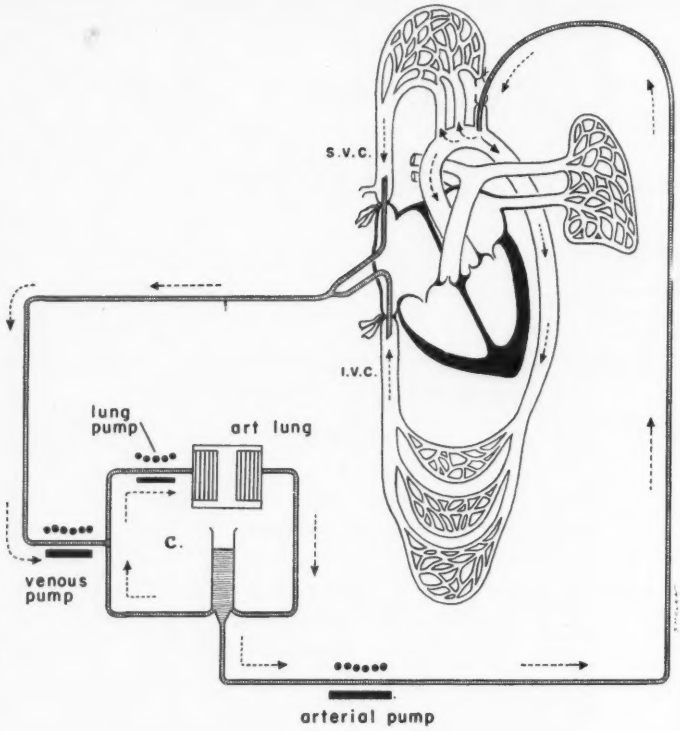

Fig. 1. Diagram showing general principles of artificial maintenance of circulation. The blood is sucked out through two cannulae from the venae cavae. It is oxygenated and is pumped back into a branch of the aorta, in this case the left subclavian artery. The flow in the proximal part of the aorta is reversed and the coronary arteries having their openings above the aortic valve are provided with blood by the machine. When ligatures are tied around the roots of the venae cavae and the azygos vein, no blood will enter the heart, except that coming from the coronary sinus and the thebesian veins.

Andreason and Watson [8,9] in England have shown that dogs survived at least 35 minutes of occlusion of both venae cavae when only the azygos vein was left open and cardiac output was reduced to 10 to 18 milliliters per kilogram of body weight per minute. Lillehei, Varco, and co-workers [10-14] have greatly advanced cardiac surgery in this country by using this principle. In dogs, they found that flow rates of 30 to 45 milliliters, as provided by cross circulation or some type of artificial heart-lung apparatus, were more suitable than the '*azygos flow*' rates of 10 to 18 milliliters per kilogram per minute. Their successful experience with 110 patients has established the principle and the procedure as being clinically valid.

The possibility of using a small flow rate revived the old idea of oxygenating blood in an apparatus using membranes. The advantages are obvious: There are no air bubbles, the possibility of air embolism is excluded; blood is not exposed to foam or screens or metal, so that potential sources of fibrin formation are eliminated.

During the earliest experience with the rotating type of artificial kidney in human beings,[15] it was observed that blue blood which entered the machine would become red during its course through the dialyzing tubing. Dubbelman[3] calculated the amount of blood that could be oxygenated in this apparatus and found that the process was impractical when high rates of blood flow were necessary. Brubaker and Kammermeyer[16] compared the gas permeabilities of various membranes and found that polyethylene is permeable to both oxygen and CO_2. Clowes[17] showed that the oxygenation of blood through a membrane of polyethylene of 1-mill thickness is much better than that through a membrane of 1.5-mill thickness. Kolff and Balzer[18] demonstrated the disposable artificial lung, here described in detail, at the first meeting of the American Society for Artificial Internal Organs in 1955. It is based on the principle of oxygenation through a polyethylene membrane. One lung unit will oxygenate 75 ml. of blood per minute; this, at a flow rate of 35 milliliters per kilogram of body weight per minute, corresponds to the requirements of a 2-kg. dog. By placing more than one unit in parallel, we can adapt the apparatus to dogs (or to children) weighing from 2 to 21 kg. (4 to 47 pounds). During use, each lung unit holds 500 ml. of blood.

This paper will describe the disposable oxygenators, the pump, the additional equipment used, and the experimental results obtained in a study of more than 130 perfusions in dogs.

Description of Apparatus

The artificial lungs. After trying out various sizes, we selected the following type of

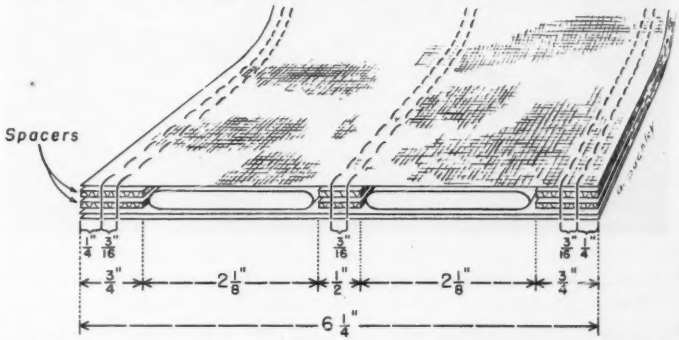

Fig. 2. Cross section of membrane arrangement of the artificial lung. There are three layers of Fiberglas window screen, two tubes of polyethylene, and three pairs of spacers (to allow space for the tubes to become distended with blood).

polyethylene lung: 7-meter long strips of plastic-coated Fiberglas screen envelope two polyethylene tubes (Fig. 2). The polyethylene tubing has a lay-flat diameter of 2 inches and its wall-thickness is 1/1000 of an inch (1 mill).* The two tubes have an oxygenating area of 14,000 sq. cm. On each side of the tubing are spacers to allow some distention of the tubing when the blood flows through it. The 7-meter long strips are specially stitched, as described for the disposable coil kidney.[19] The strips are wound around a can (10 cm. in diameter) and are provided with inlet and outlet tubing, also identical to those used in the coil kidney. The completed coil (Fig. 3) is placed in an ordinary transparent plastic bag, such as that used for vegetables. Oxygen is blown into the bottom part of the artificial lungs at a rate of 30 liters per minute (for eight lungs). It is heated to approximately 40 degrees C. in a copper coil immersed in a constant-temperature water-bath. A string is tied around the top of the bag, just tightly enough so that oxygen flow will distend the bag, but loosely enough so that CO_2 and excess oxygen may escape through the top. The lungs are prefabricated and sterilized with ethylene oxide by Baxter Laboratories,** and can be kept sterile until needed. Since the lung units are contained in transparent plastic bags, a blood leak can be seen. A small pinhole leak does not interfere with use of the lung, but if a large leak develops, that particular unit must be replaced. The lungs are pretested at the factory, and in our experience only one in approximately 80 units had to be replaced because of leaks.

The pumps. We use the same type of commercially available finger pump as that used by Lillehei and co-workers. For the arterial and venous pumps we use a dual Model

Fig. 3. Artificial lung (right) and artificial lung in a plastic bag with tube for oxygen inlet at the bottom.

* *Polyethylene tubing was provided by Visking Corp., 6733 West 65 Street, Chicago 38, Illinois, through the courtesy of Mr. W. E. Henderson, Assistant Manager of the Plastic Film Development Department.*

** *Baxter Laboratories, Morton Grove, Illinois.*

T 6 F Sigmamotor Pump.* The variable-reduction transmission in this pump has been provided with dials for calibration (Fig. 4) by Mr. Frederick Olmsted of the Research Division. A third pump or "lung pump" is used for the lung circuit. This pump is a single Model T 6 F Sigmamotor Pump.*

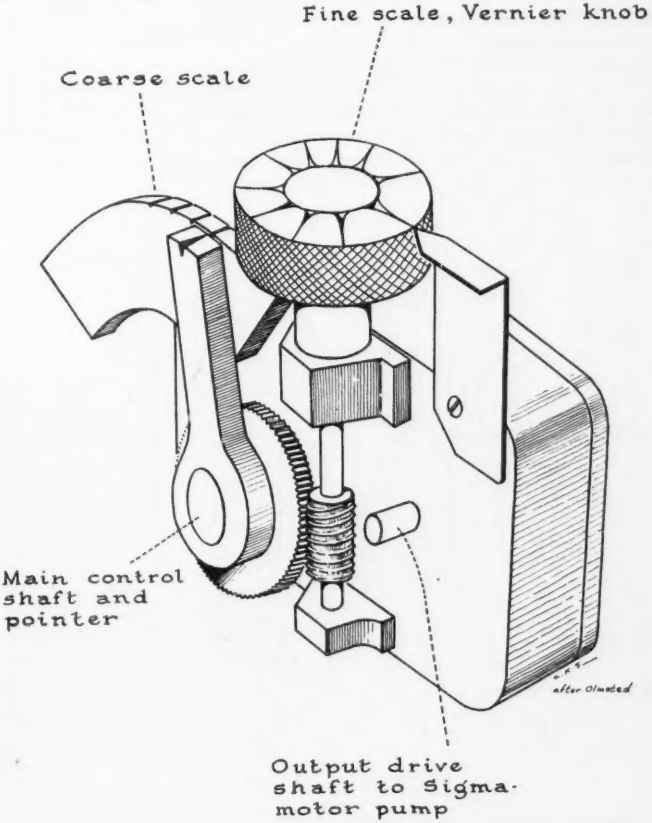

Fig. 4. Calibration adjustor made by Mr. Frederick Olmsted for the variable-speed reduction transmission of the blood pumps.

The blood circuit. In order to maintain a constant volume of blood in the oxygenator system we have adopted the third pump, as did Miller, Gibbon, and Gibbon.[5]

The center section of Figure 5 outlines the lung circuit. The first step is to recirculate blood through this circuit at a constant rate. The lung pump is set to provide a flow slightly in excess of the maximal flow planned for the experiment. Blood travels through the lungs and is collected in a manifold made from a plastic bag similar to a blood-trans-

* *Sigmamotor, Inc., Middleport, New York.*

fusion bag. Since flow through the lungs, resistance in them, and the volume of blood that accumulates in them are stable, the blood in the collecting manifold assumes a constant level. This level can be adjusted by raising or lowering the attached burette. Polyethylene is permeable to oxygen and CO_2 but is almost impermeable to water, so that there is no appreciable loss through evaporation. Although changes in volume of as little as 20 ml. can be detected, we have found that the blood level in the manifold remains stable over several hours.

To establish an artificial circulation, the arterial pump is set at a predetermined rate (usually 35 ml. per kg. of body weight per minute) and the venous pump is adjusted so that rates of inflow and outflow are identical, as judged from the level in the collecting manifold. Since the volume of blood in the manifold and burette is large, accidental sudden reduction of inflow does not immediately deplete blood from the machine or

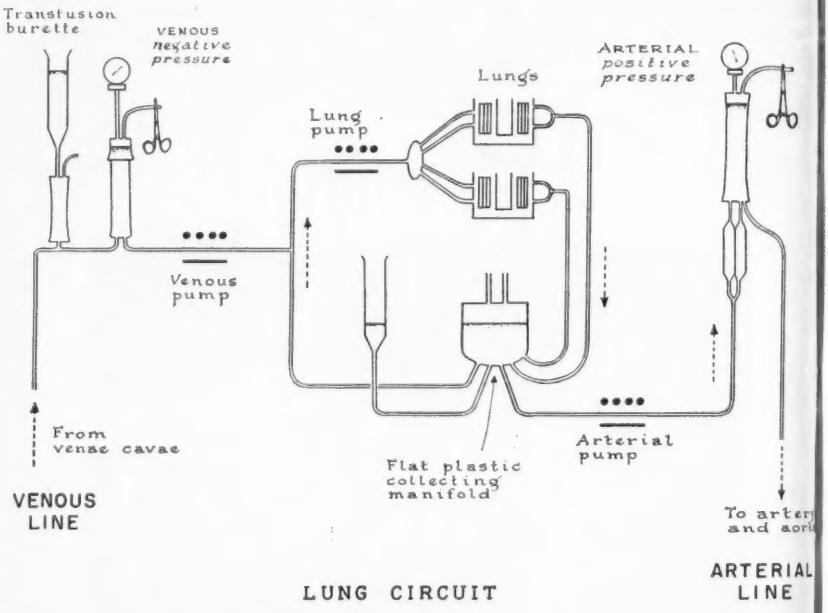

Fig. 5. Artificial heart-lung circuit. Blood coming from the venae cavae passes a bubble catcher with a negative-pressure manometer that indicates the degree of suction. The venous pump delivers the blood into the lung circuit. The arterial pump at right, pumps the oxygenated blood out of the circuit through two filters, and a bubble catcher with a positive-pressure manometer. This manometer indicates the animal's blood pressure when the pump is not running. It will indicate the sum of the animal's blood pressure, plus the pressure necessary to overcome the resistance in the arterial lines and cannulae while the pump is running. In the center of the figure is the lung circuit. The lung pump is set at a rate slightly higher than the highest rate at which the arterial pump will work in the particular experiment. The speed of the lung pump is not changed; with both venous and arterial pumps not running, an equilibrium is established and the blood in the collecting manifold stays at the same level. When the venous and arterial pumps are started and the level is maintained, input and output of the machine are exactly alike.

result in air embolism. When reduction of inflow does occur, it usually indicates that the dog has lost too much blood, so that caval flow is inadequate. When this is the case, the dog is transfused from the transfusion burette. Inadequate caval flow or obstruction of venous catheters may be recognized from an excessive negative pressure in the manometer attached to the bubble-catcher in the venous line.

Details of the arterial line, the venous line, and the manifold that distributes the blood over several lungs are shown in Figures 6, 7, and 8. The only parts of the heart-lung machine that are not yet provided by the Baxter Laboratories at this time are two silicone-coated burettes and the rubber tubing that fits in the pumps.

Blood used. Blood is drawn into siliconized blood-transfusion bottles* containing 12 mg. of heparin in 30 ml. of a diluent consisting of glucose 2½ per cent, and sodium chloride 0.45 per cent in water. Each bottle received 500 ml. of blood. Usually the blood is collected by puncture of the femoral artery. If the artery has to be prepared under local anesthesia, succinylcholine, 10 to 20 mg. is used,† rather than a barbiturate which might pass via the blood into the 'patient' dog.

It is unnecessary to fill the machine with saline prior to use. The equipment is assembled dry and it is directly primed with blood. This avoids undesirable dilution of the donor blood with saline. We need approximately 500 ml. of blood for each lung unit that

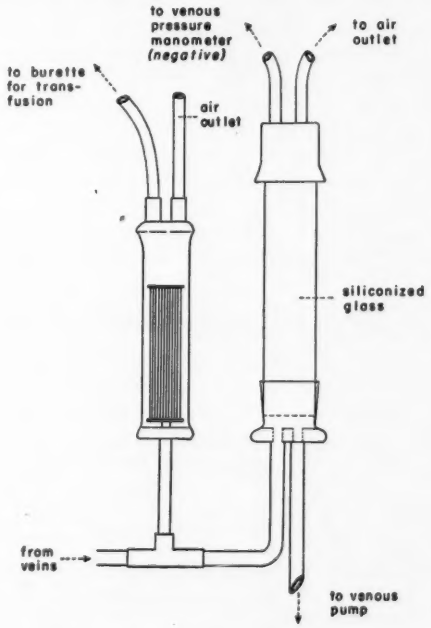

Fig. 6. Venous inflow line, with a filter for blood that enters from the transfusion burette (made by Baxter Laboratories).

* *Provided through the courtesy of Baxter Laboratories.*

† *Respiration is maintained with a respirator.*

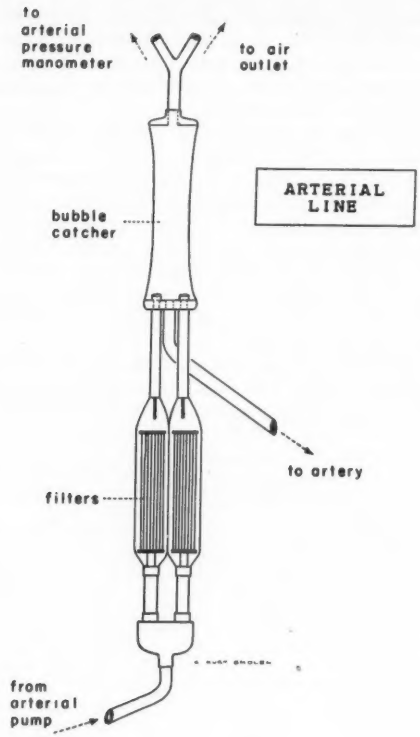

Fig. 7. Arterial outflow lines have two filters and a bubble catcher (made by Baxter Laboratories).

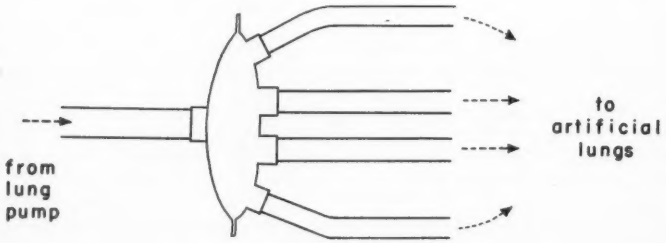

Fig. 8. A lung manifold. We have other manifolds for eight lung units (made by Baxter Laboratories).

is used, plus 500 ml. to fill lines, circuits, and burettes.

The blood lost during operation is collected in a measuring cylinder that is coated with silicone so that the volume can be measured accurately without being obscured by foam. An equivalent volume of blood is replaced and an additional 15 ml. per kilogram of body weight is transfused during each run.

Technic

Anesthesia. Preoperative medication: Procaine penicillin, 400,000 units, and streptomycin, ½ gm., are administered on the day before and on the day of the experiment. Morphine, 5 to 15 mg. depending on the weight of the dog, is administered one or two hours before operation.

Induction: One per cent thiopental (Sodium Pentothal) is administered intravenously in small interrupted doses, for endotracheal intubation, in an average total dose of 10 mg. per kg. of body weight. This anesthesia is supplemented with succinylcholine, diluted 1 mg. per ml., given intravenously in intermittent doses (total 0.5 to 1 mg. per kg. of body weight) to maintain diaphragmatic relaxation. Controlled respiration with 100 per cent oxygen is maintained throughout the procedure except while the cavae are occluded. Immediately prior to connection with the machine, the dog is hyperventilated; but during the actual run, the lungs are permitted to remain 50 per cent collapsed. Since anesthetic agents given to the dog intravenously during the run would be sucked into the machine, they are injected as needed into the arterial outflow line from the machine. Ninety per cent of the animals require no more anesthesia during or after the run. Light anesthesia is preferred so that the dog is moving at the end of the procedure, permitting adequate and immediate evaluation.

Operative technic. In the early experiments, testing of the oxygenator was the main purpose, and cannulation was performed from the neck. A long plastic cannula with side openings was inserted from the external jugular vein through the right atrium into the vena cava caudalis. Ligatures were tied around the venae cavae where they enter the atrium, and around the azygos vein. Thus, all venous flow into the heart was closed off before the heart was opened. (There were side holes in the catheter where it lay in the cranial and caudal venae cavae.) The blood was returned to the arch of the aorta through a cannula inserted through a carotid artery. The chest was opened in the fourth or the fifth intercostal space on the right side.

To train the surgical team for the intrathoracic cannulation and to simulate the procedure that later would be used in human infants, transverse thoracotomies were performed. The venae cavae were cannulated from the right auricle, and the aorta from the left subclavian artery. The technic has been described by Lillehei and co-workers, and the cannulae that we used are like theirs.* After the technic of cannulation had been mastered, we returned to inserting the arterial cannula through the cervical portion of the carotid, in order to avoid

**Pharmaseal K-60 expendable, plastic suction catheter Size 14 French.*
Pharmaseal K-21 expendable, plastic oxygen catheter Size 10 French.
Pharmaseal Laboratories, Glendale 1, California.

the transverse thoracotomy. Healing of a transverse thoracotomy, especially in large dogs, is difficult.

Postoperative care. All dogs were observed for at least six hours postoperatively. The administration of meperidine hydrochloride sometimes was necessary to keep the dogs quiet during the postoperative hours when they were kept on the table to facilitate recording of blood pressure, aspiration from the chest tube, and transfusion of blood if necessary. The tip of the chest tube should be in the dorsal part of the chest cavity, just above the diaphragm, and the dog should lie on the side in which the catheter is inserted. During the first three or four hours after operation, the dogs received a continuous infusion with protamine sulfate and sodium bicarbonate, as will be described later.

Table 1.—*Results of experiments with artificial heart-lung machine*

Lig. of V.C.	Rt. aur. opened	Rt. vent. opened	I.A.S.D. made and closed	I.V.S.D. made and closed
+	—	+	—	—
—*	—	—	—	+
+	+	—	—	+
+	+	—	—	+
+	+	—	+	+
+	+	+	—	—
	+	—*	—	+
	+	+	—	
	+	+	+	
			+	
			+	
			—	

Each + or — represents one dog.
+ Dog survived and recovered completely.
— Dog died within two days after the operation.
*—*Dog died more than one week after the operation.*

Results

Mortality. Table 1 pertains to the work done before the first of November 1955 and presents results with 43 dogs consecutively treated with various operative procedures. It is evident that each new procedure in the beginning took its toll. Later, when we began to perform transverse thoracotomies, and when we practiced on very small pups (the smallest weighed 1.2 kg.), we again had a high mortality.

The late mortality in dogs for the most part was caused by pleural effusion or wound infection with empyema. Some late deaths were due to atelectasis of one lung, caused by an air leak or mucus in the bronchus.

Before attempting elective potassium arrest, which will be discussed in the following article, we had performed seven consecutive experiments, in all of which the right ventricle was opened and in all of which the dogs recovered.

Hemolysis. Dog blood hemolyzes readily, and the extent of hemolysis largely depends on the method of drawing the blood. A survey of the influence of hemolysis on survival, on the occurrence of hemoglobinuria, and on the increase of plasma hemoglobin was made during the early experiments of this series. It was found that the plasma hemoglobin contents of 23 dogs that survived, ranged from 84 to 360 mg. per hundred milliliters (average 195 mg.); those of four dogs that died, ranged from 144 to 306 mg. per hundred milliliters (average 222 mg.). There were no indications that a high plasma hemoglobin had any ill effects, although we consider it undesirable. Often four dogs were treated on the same day with the same blood in the machine. The plasma hemoglobin in the machine was determined at the beginning and at the end of the day. The increase was less than 20 mg. per hundred milliliters after a whole day on six of nine occasions. Hemoglobinuria never was observed, although all dogs were placed on white cellucotton sheets after the experiments. In the more recent experiments of this series, good control over hemolysis was achieved by drawing the blood into siliconized bottles* and by avoiding the formation of foam (Table 2).

In the early experiments the oxygen content of the blood was determined by the Van Slyke method† (Table 3). It was established that one lung unit could oxygenate 75 ml. of blood per minute. In the more recent experiments the percentage of oxygenation was determined with the reflex oxymeter of Brinkman.[20]** When the small-flow principle is used, the oxygen saturation of venous blood is extremely low, which puts high demands on the capacity of the oxygenator. However, the oxygen saturation of the arterial blood still was more than 90 per cent. Some determinations are presented in Table 4.

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* *Baxter Laboratories, Morton Grove, Ill.*

† *Determinations were made in the laboratory of F. Mason Sones, Jr., M.D., in the Department of Cardiovascular Disease.*

** *Manufactured by Kipp in Delft, Holland.*

Table 2. *— Plasma and blood hemoglobin in gm./100 ml. (Free plasma hemoglobin as indicator of hemolysis during treatment with heart-lung machine)*

Experiment No.	Total duration of functioning of artificial heart-lung	Surgical intervention	Dog before	Machine before	Dog end	Machine end	Dog 1 hour later	Comment
125	15 min. connection. Recirculation time before 30 min.	Interventricular septal defect made and closed	Plasma Hb. . . . 0.018 Blood Hb. 12.5	0.030 12.8	0.018 8.3	0.024 9.2	0.018 8.1	Recovered
127	22 min. connected. Recirculation time before 20 min.	Elective K arrest; interventricular septal defect made and closed	Plasma Hb. . . . Blood Hb. 14.4	0.042 14.7	0.036 13.0	0.42 12.1	0.066* 12.3	Recovered
132	31 min. connected. Recirculation time before 15 min.	Elective K arrest; ventriculotomy and auriculotomy	Plasma Hb. . . . 0.036 Blood Hb. 13.7	0.024 12.7	0.054 14.0	0.042 13.2	0.054 12.3	Recovered
135	46 min. connected. Recirculation time before 15 min.	Elective K arrest; ventriculotomy	Plasma Hb. . . . 0.054 Blood Hb. 18.3	0.042 12.5	— 12.2	0.054 11.3	0.066 10.3	Recovered

** Higher plasma hemoglobin 1 hour postoperatively probably was caused by difficulty of drawing samples from cannula. Anemia in first dog was caused by dilution of blood in the machine with saline.*

Table 3.—*Oxygen uptake of blood during oxygenation in artificial heart-lung machine, determined at the end of the experiment*

Experiment No.	Flow rate, ml./min.	Number of lungs	O_2 venous blood	O_2 arterial blood	O_2 capacity
48	300	4	6.2 vol. %	14.4 vol. %	15.9 vol. %
51	280	4	6.9 vol. %	12.9 vol. %	13.3 vol. %
59	300	4	—	14.5 vol. %	15.5 vol. %

Table 4.—*Oxygen saturation in blood coming from the artificial heart-lung machine, determined at the end of the experiment*

Experiment No.	Flow rate, ml./min.	Number of lungs	O_2 saturation
112	300	4	96%
113	300	4	98%
114	300	4	94%
120	150	2	95.5%
133	350	4	92%

Acidosis (pH and CO_2).* (Table 5) Acidosis may be expected in anesthetized dogs.[21] Following the method of Swan and associates[22] and Osborn,[23] we hyperventilated the dogs prior to connecting them to the heart-lung machine. This lowered the carbon dioxide content and often overcorrected blood pH so that alkalosis resulted. A further metabolic acidosis must be expected during extracorporeal maintenance of circulation, especially when the small-flow principle is followed.[24]

CO_2 is effectively removed from circulating blood in the heart-lung machine; this is most evident in the donor blood that has been recirculated through the heart-lung machine for some time. It loses about one half of its CO_2; however, the pH of this blood is only slightly altered. We have also shown the changes of CO_2 and pH during the experiments in dogs treated or untreated with $NaHCO_3$. Before we administered $NaHCO_3$, the metabolic acidosis was evident. With $NaHCO_3$ this acidosis could be corrected or overcorrected as in experiments 128, 129, 130 (Table 5).

* *Most of the chemical determinations were made under the personal supervision of A. Hainline, Jr., Ph.D., and by Miss Victoria Asadorian, of the Department of Clinical Pathology.*

Table 5.—*Changes in pH and in CO_2 during experiments with heart-lung machine. (In the later experiments pH was corrected with $NaHCO_3$.)*

Experiment No.	Duration of arterial circ. with venae cavae occluded	pH, CO_2 Venous blood from dog		Blood recircul. in machine before connect.	$NaHCO_3$ into machine during run, mEq./kg.	pH, CO_2 Venous blood from dog, end	pH, CO_2 Blood from machine at end	$NaHCO_3$, mEq./kg., postop. infusion	pH, CO_2 Venous blood from dog 1 hr. postop.	More than 1 hr. postop.	Next morning	Comment
		Onset anesth.	Before connect.									
123	20 min.	7.32 20.6 m.mol.	7.58 7.4 m.mol.	7.39 5.7 m.mol.	None		7.20 10.0 m.mol.	None	7.26 15.5 m.mol.	7.37 15.5 m.mol.	7 40 16.3 m.mol.	Recovered
124	10 min.	7.22 18.2 m.mol.	7.55 12.7 m.mol.	7.35 7.4 m.mol.	None	7.33 10.8 m.mol.	7.31 9.1 m.mol.	2 mEq./kg.	7.28 21.0 m.mol.	7.31 24.0 m.mol.	7.33 21.4 m.mol.	Recovered
125	10 min.		7.46 12.5 m.mol.		None	7.24 10.4 m.mol.	7.25 11.6 m.mol.	2.5 mEq./kg.	7.12 18.2 m.mol.			Recovered
127	19 min.		7.34 17.2 m.mol.	7.41 12.5 m.mol.	None	7.37 15.5 m.mol.	7.24 15.5 m.mol.	11 mEq./kg.	7.34 30.3 m.mol.			Elective K arrest; recovered
128	14 min.		7.49 12.9 m.mol.	7.33 9.1 m.mol.	7.5 mEq./kg.	7.34 20.6 m.mol.	7.35 17.2 m.mol.	7.5 mEq./kg.	7.42 30.3 m.mol.			Elective K arrest; recovered
129	14 min.		7.64 11.2 m.mol.	7.42 11.2 m.mol.	4 mEq./kg.	7.39 19.3 m.mol.	7.38 14.6 m.mol.					Elective K arrest; accidental death
130	19 min.		7.51 10.0 m.mol.	7.46 13.0 m.mol.	7 mEq./kg.	7.32 24.1 m.mol.	7.32 23.2 m.mol.	7 mEq./kg.	7.56			Elective K arrest; died from empyema after 8 days
132	26 min.			15.0 m.mol.	4.5 mEq./kg.	7.4	7.38 24.6 m.mol.	4.5 mEq./kg.	7.48 20.8 m.mol.			Elective K arrest; recovered
135	42 min.		12.5 m.mol.	15.5 m.mol.	5 mEq./kg.	18 m.mol.	17.5 m.mol.	5 mEq./kg.	29 m.mol.			Elective K arrest; recovered

We now routinely administer a continuous drip of sodium bicarbonate during the run, 4.5 mEq. per kg. of body weight. It is made up to 100 ml. with 5 per cent fructose in water and is administered into the collecting manifold during the run. This seems to bring both pH and CO_2 to normal levels. A second dose of 4.5 mEq. of sodium bicarbonate per kg. is administered in the course of three hours postoperatively. It is made up to 100 to 300 ml. with 5 per cent fructose in water to which 25 or 50 mg. of protamine sulfate is added. Thus, pH and CO_2 levels are maintained at the expense of a slight increase of serum sodium.

Changes in serum sodium and serum potassium (Table 6). The slightly elevated serum sodium of blood in the machine is caused by the 40 ml. saline solution used as diluent for the heparin in the blood-collecting bottles. An alternative would be to put 30 or 40 ml. of 5 per cent glucose in the bottles, but this would lead to blood sugar levels of at least 380 or 480 mg. per hundred milliliters in the machine and almost the same instantaneously in the dog. As this may be undesirable we recently used 0.45 per cent saline solution and 2½ per cent glucose as diluent for the heparin.

The $NaHCO_3$ injected during the run seemed to have little effect on serum sodium; however, postoperatively the same dose tended to increase serum sodium, although still within the range of normal variations. The serum potassium posed no problem, not even in dogs that underwent elective cardiac arrest with potassium citrate.

Temperature. The oxygen going into the artificial lungs was heated to 40 degrees C., but no other heating for the blood in the machine is provided. Consequently, the dogs showed a fall in body temperature often to 34 degrees C. during the run, which was counteracted with a heating pad (care was taken to avoid burns).

Disturbances in clotting mechanism. The tendency of the animal to bleed has created difficulties for numerous investigators in this field. We also have lost a number of dogs from oozing or diffuse hemorrhage. In our recent experiments this complication has become rare. Heparin has been given: 0.8 mg. per kg. of body weight to the dogs and 12 mg. per 500 ml. of blood. The blood was collected in siliconized bottles (Baxter) with 30 or 40 ml. of saline solution or 5 per cent glucose as diluent. Heparin was neutralized with protamine sulfate (Upjohn), 25 mg. for small and 50 mg. for large dogs. This was followed by a continuous intravenous infusion of the same amount of protamine sulfate to prevent 'heparin rebound.'

Heparin rebound. This is a treacherous hemorrhagic phenomenon. When heparin is neutralized by protamine sulfate, the clotting time becomes normal in a matter of minutes. However, protamine sulfate seems to be eliminated from the blood stream before heparin is, thus leaving the heparin uncovered, as demonstrated by protamine titration. The following is an example of heparin rebound.

Table 6.—*Serum Na and K changes (in mEq./l.) in dogs during and after treatment with the heart-lung machine (in the later experiments pH was corrected with $NaHCO_3$ as indicated, and in the last five there also was elective cardiac arrest; serum Ca and P (in mg.%) in one dog).*

Experiment No.	Duration of artificial circulation with venae cavae occluded	Venous blood from dog, before	Blood circulating in machine just before connection	Elective K arrest	$NaHCO_3$ into machine	Venous blood from dog, end of run	Blood from machine	$NaHCO_3$ given as postoperative infusion	Venous blood from dog 1 hour later	Venous blood from dog next morning	Comment
123	20 min.	Na 145 K 3.3 Cl 118 Ca 9.6 mg.% P 3.5 mg.%	Na 131 K 3.9 Cl 106 Ca 7.0 mg.% P 3.3 mg.%	No	None	—	Na 131 K 3.7 Cl 106	None	Na 139 K 3.4 Cl 110	Na 133 K 4.3 Cl 110 Ca 8.7 P 4.1	Recovered. Blood collected in transfusion bottles with glucose
124	10 min.	Na 145 K 3.5	Na 150 K 3.2	No	None	Na 155 K 3.4	Na 150 K 3.5	2 mEq./kg.	Na 160 K 3.9	Na 143 K 4.0	Recovered
128	14 min.	Na 148 K 4.3	Na 153 K 3.7	Yes ± 0.5 gm.	7.5 mEq./kg.	Na 162 K 3.2	Na 162 K 3.9	7.5 mEq./kg.	Na 168 K 2.9		Recovered
129	14 min.	Na 145 K 3.7	Na 148 K 4.0	Yes 0.25 gm.	4 mEq./kg.	Na 140 K 3.4	Na 135 K 3.5				Accidental death
130	19 min.	Na 155 K 4.0	Na 147 K 3.1	Yes 0.375 gm.	7 mEq./kg.	Na 157 K 2.9	Na 156 K 3.1	7 mEq./kg.			Died from empyema 8 days postoperatively
132	26 min.	Na 148 K 3.7	Na 150 K 4.2	Yes ± 0.25 gm.	4 mEq./kg.	Na 143 K 3.5	Na 147 K 3.4	4 mEq./kg.	Na 153 K 3.3		Recovered
135	46 min.	Na 143 K 3.8	Na 150 K 4.0	Yes 0.2 gm.	4.5 mEq./kg.	Na 148 K 3.9	Na 153 K 3.2	4.5 mEq./kg.	Na 158 K 4.4		Recovered; second dose of K required for ventricular fibrillation

The average of 73 determinations of serum Na in normal dogs in our laboratories was 144 (138—164) mEq./l.
The average of 69 determinations of serum K in normal dogs in our laboratories was 3.7 (3—4.6) mEq./l.

Experiment 101. The dog weighed 8.3 kg. Surgical procedure: interventricular septal defect made and closed. Thrombocytes before the experiment were 260,000 and afterward were 230,000 per cu. mm. Heparin dosage was as usual, 12 mg. for each bottle of blood to fill the machine and 0.8 mg. per kg. into the dog at onset. It was estimated that for a blood volume of 800 ml. there was not more than 20 mg. of heparin in the dog at the end of the experiment. Twenty-five milligrams of protamine sulfate was given at the end of the surgical procedure. Clotting time 15 minutes later was nine minutes. However, when protamine sulfate was added for a protamine titration test, all tubes clotted within five minutes. During the next hour, loss of blood necessitated transfusion of 280 ml. citrated (nonheparinized) blood. An additional amount of 10 mg. of protamine sulfate was given; however, one hour later the blood would not clot at all. Protamine titration indicated no clotting except in the two last tubes with the highest concentrations of protamine sulfate. Twenty milligrams of protamine sulfate given intravenously was of no avail; there was no clotting. Seventy milligrams of protamine sulfate given intravenously thereafter reduced the clotting time to 10 minutes (the clot was solid). The clotting time remained 9 or 10 minutes for the next eight hours. The dog was able to walk through the laboratory, but it continued to bleed into the chest and finally died. The cause of the hemorrhage could not be determined. We know from experience with patients who have been treated with the artificial kidney that oozing may continue long after the clotting time has returned to normal.

Thrombocytes. Orienting experiments with our oxygenator, performed during a visit to Doctor Lillehei's laboratories, showed that it caused transient falls in white blood cell and platelet counts of peripheral blood. The transient fall in platelet counts was confirmed in later experiments (Table 7) but did not

Table 7. *– Platelet count per cubic millimeter of blood before and after treatment with the artificial heart-lung*

Experiment No.	Duration of perfusion	Type of operation	Dog blood before	Machine before	Dog after	Machine after	Dog after 1 hour	Comment
103	15 min.	I.V.S.D.	—	180,000	250,000	240,000	300,000	3 hr. later, 290,000. Died 10 days p.o. of wound infection
132	31 min.	Elective cardiac arrest; ventriculotomy and auriculotomy	290,000	—	180,000	160,000	300,000	Recovered

always occur. Within one hour the platelet counts were back to normal. The excellent clot retraction after administration of protamine sulfate also indicated normal platelet function. When the heparin was neutralized with an estimated dose of protamine sulfate* the adherence of the blood clot to an applicator stick could be studied (Fig. 9). It may be seen that during the one run, at least in one experiment, adherence was poor, although it was back to normal within 15 minutes.

* *This work was done by Cecil M. Couves, M.D., who was working as a guest in our laboratory.*

The average of 73 determinations of serum Na in normal dogs in our laboratories was 144 (138 – 164) mEq./l.
The average of 69 determinations of serum K in normal dogs in our laboratories was 3.7 (3 – 4.6) mEq./l.

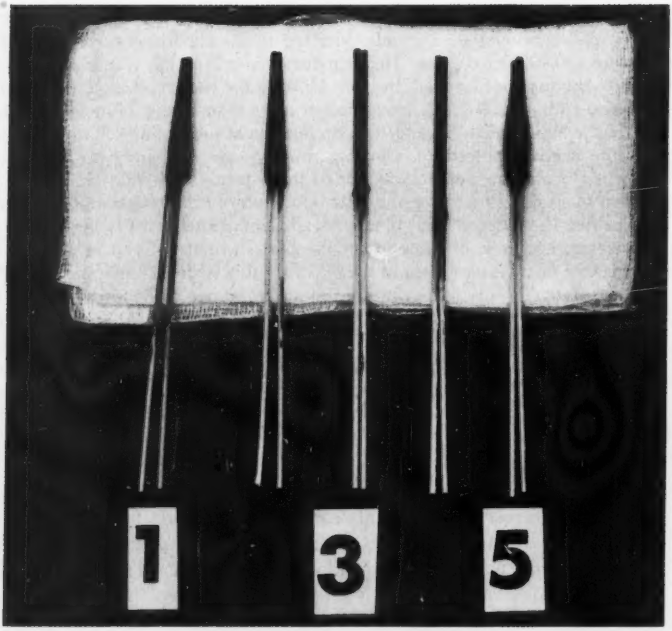

Fig. 9. Demonstration of clot formation before, during, and after an experiment. Applicator sticks have been placed in blood samples and have been removed after the blood was clotted (*Cecil M. Cowes, M.D.*). No. 1—Clot before the dog had been heparinized. No. 2—Clot after the dog had been heparinized, but heparin was neutralized with protamine sulfate in the sample. No. 3—Blood from the machine, showing only a very minute clot adherent to the sticks, despite the fact that heparin in the sample had been neutralized with protamine sulfate. No. 4—Blood from the dog toward the end of the experiment, while the dog still was connected to the machine; heparin in the sample also had been neutralized. No. 5—Clot from the dog's blood 15 minutes after the experiment and after the administration of protamine sulfate to the dog. The clot is normal.

Prothrombin times. During treatment with the artificial heart-lung, prothrombin times changed no more than might be expected from hemodilution (Table 8). This excludes damage to the early phases of the clotting mechanism in the two experiments studied.

Bleeding time. Stabbing with a hemolet into the undersurface of the dog's tongue at the end of the experiment and after administration of protamine sulfate did not reveal a prolongation of the bleeding time in any of the dogs in which it was tested.

The general conclusion in regard to clotting mechanisms with this type of artificial heart-lung is that when heparin is adequately neutralized with protamine sulfate, only transient changes in the clotting mechanism occur. Within 15 minutes the changes revert to normal. However, the use of old blood,

Table 8.—*Prothrombin times before, during and after treatment with the artificial heart-lung*

Experiment No.	Duration of perfusion	Type of operation	Prothrombin times in sec., and hemoglobin in gm./100 ml.					Comment
			Before	After heparinization *	Blood from machine at end *	Blood from dog at end *	Blood from dog **after 15 min.	
125	15 min.	I.V.S.D.	6 sec. Hb.12.5gm.	9 sec. Hb.12.8gm.	11 sec. Hb. 9.2 gm.	—	8 sec. Hb. 8.3 gm.	Recovered
127	22 min.	Elective cardiac arrest; I.V.S.D.	8 sec. Hb.14.4gm.	9 sec. Hb.14.7gm.	10 sec. Hb. 13 gm.	10 sec. Hb. 12 gm.	8 sec. Hb.12.3gm.	Recovered

* *Protamine sulfate added to sample.*
** *Dog had received usual amount of protamine sulfate.*

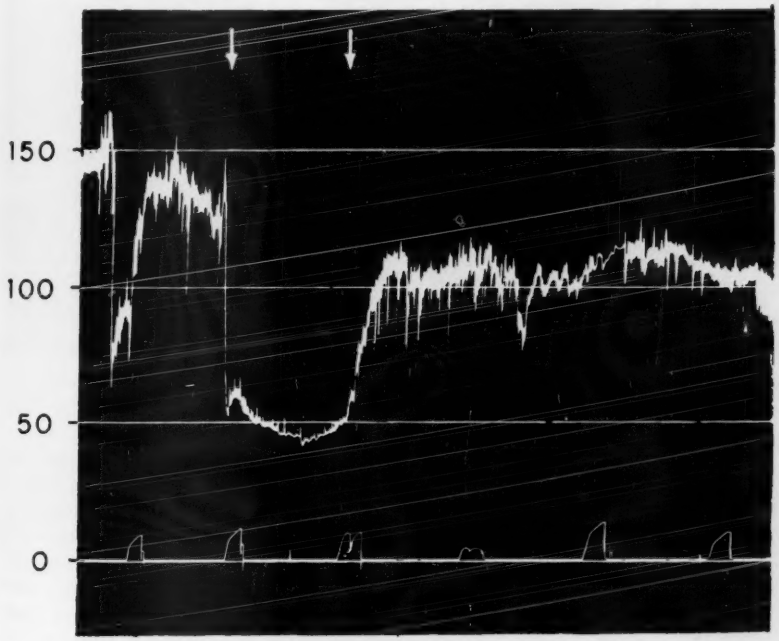

Fig. 10. Experiment 55. Arterial blood pressure is indicated in mm. Hg. Time is indicated at the bottom in 10-minute intervals. At the first arrow, the artificial heart-lung is started and ties are put around the venae cavae. There is a sharp drop in arterial pressure and during the following minutes the right ventricle is opened. It is closed, and at the second arrow the ligatures are removed from the venae cavae. Blood pressure rises to about 100 mm. Hg within a few minutes.

large amounts of dextran, or failure to clean parts of the machine affect the clotting mechanism disastrously.

Arterial blood pressure. During the extracorporeal circulation at low flows, the blood pressure falls more or less sharply when the venae cavae are occluded (Fig. 10) and in successful experiments rises again after release of the ligatures. Sometimes it takes 15 minutes for the blood pressure to be restored (Fig. 11).

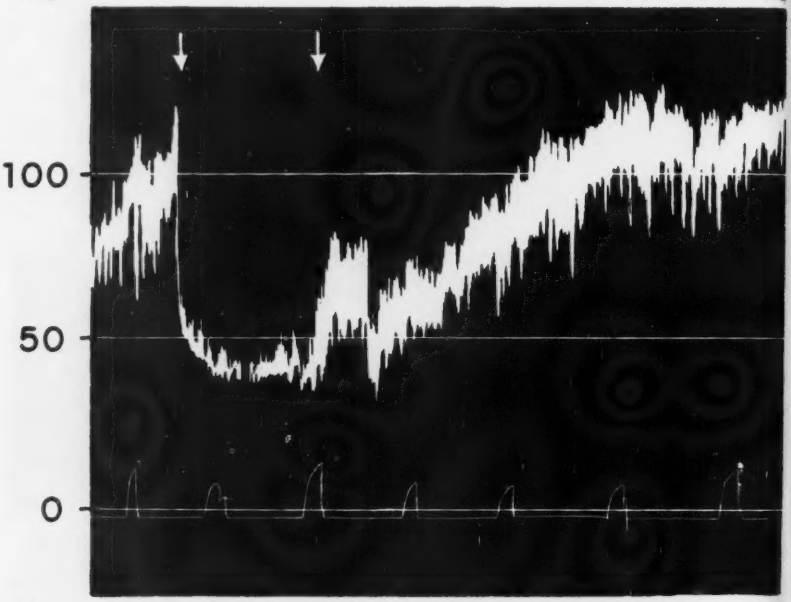

Fig. 11. Experiment 72. An interventricular septal defect is made and closed. At the second arrow the ligatures around the venae cavae are released, but it takes the blood pressure about 15 minutes to rise to 100 mm. Hg.

In some dogs we have observed a late fall in blood pressure which could not be explained on the basis of loss of blood. It is akin to the fall in blood pressure that Olmsted and Kolff observed several years ago after replacement transfusion in dogs. It usually responds well to additional transfusion (Fig. 12). When it is not corrected it leads to respiratory arrest. Some dogs have required the administration of mephentermine sulfate (7½ mg. in a 10-kg. dog) or a continued infusion of norepinephrine to help them over a period of low blood pressure that could not be explained on the basis of loss of blood, and could not be corrected by blood transfusion alone.

Venous blood pressure. The continuous observation of the venous blood pressure during the postoperative course has been very helpful in some cases when trouble arose. Prior to anesthesia and under local anesthesia, a plastic cannula is inserted in the femoral vein and is moved up until its tip almost

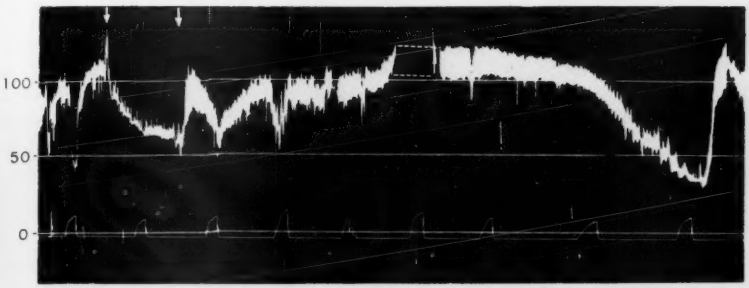

Fig. 12. Experiment 64. An auricular septal defect is made and closed. After release of the venae cavae at the second arrow, the blood pressure starts to rise. There is a temporary fall that possibly is due to protamine sulfate. The blood pressure rises again, but about one hour after termination of the experiment it falls again. When it was detected it could easily be corrected with infusion of blood, although the fall could not be explained on the basis of loss of blood.

reaches into the chest. This catheter later is used for the administration of intravenous anesthetics, draining of blood samples, the administration of a continuous drip in the immediately postoperative stage, and occasionally it has been used as the venous cannula if the dogs were reconnected to the machine for a second run. When both the venous pressure and the arterial pressure are low, the dogs should most likely be transfused. When the venous pressure is high while the arterial pressure is low, the cause of trouble should be other than loss of blood. It may be that the closure of the pericardium over the distended heart is too tight or it may be failure of the right ventricle.

"Second run." Thirteen dogs had low arterial blood pressure after the experiments, which evidently was due to cardiac failure. Extensive cutting into the interventricular septum probably was the cause. It has been possible to bring them into better condition by reconnecting them to the artificial heart-lung, leaving caval flow intact and using either the original cannulae or peripheral cannulation. In some dogs the artificial heart-lung was restarted two or three times. One dog was reconnected to the machine five hours after completion of the first experiment. A detailed history of this dog follows.

Experiment 125. The dog weighed 8.5 kg. The venae cavae were cannulated from the auricle; the aorta was cannulated from the right carotid artery. After the artificial heart-lung had been started and the venae cavae had been occluded, the right ventricle was opened and a large interventricular defect was made and closed. The right ventricle was closed. The superior vena cava was opened and two minutes later the inferior vena cava was opened. After 15 minutes the artificial heart-lung was stopped; blood balance was made and proved to be 200 ml. in favor of the dog. Blood pressure was 130 mm. Hg, protamine sulfate, 25 mg., was given, the heart was not distended, clotting time was 11 minutes. Infusion of $NaHCO_3$ was started. After about one hour, the electrocardiogram revealed complete atrioventricular block (Fig. 13). The dog's condition gradually deteriorated. The ventricular rate was 60, blood pressure was 55 mm. Hg, although 45 ml. of blood aspirated from the chest had been replaced by transfusion. The venous pressure ranged from 6 to 9 cm. of water. The clotting time was four minutes. Blood

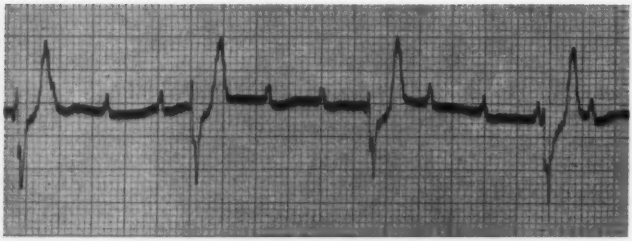

Fig. 13. Experiment 125. Electrocardiogram of the dog taken in the interval between the first and second treatments with the artificial heart-lung. There is a complete A.V. block showing Q waves and abnormal QRS complexes. The ventricular rate is 57, the auricular rate is 180 per minute.

pressure continued to go down, and four hours after the operation it was 44 mm. Hg. The dog that had been alert and awake before, gradually was becoming unconscious. Since in our experience dogs will not do well if they are allowed to have a low blood pressure for a long time, an infusion of norepinephrine, 4 ml. (1 mg.) in 750 ml. 5 per cent fructose was started. This brought the blood pressure up to 60 to 85 mm. Hg.

In the meantime a second dog had been treated with the heart-lung machine. Five hours after the original experiment, while the first dog's condition obviously was steadily deteriorating and it still had the atrioventricular block, it was reconnected to the artificial heart-lung. The venous cannula that previously had been inserted through the femoral vein into the vena cava caudalis and the arterial cannula in the right carotid artery were used. The flow was approximately 220 ml. per minute. No further anesthesia was used, and perfusion was continued for 32 minutes. After that the blood pressure was constant at about 75 mm. Hg without medication. A half hour later, the pulse rate suddenly rose to 84 beats per minute, and the blood pressure rose to 100 mm. Hg. Later the pulse rate rose to 176 beats and the blood pressure to 120 mm. Hg. Two hours after the second perfusion the dog was walking about in the laboratory. The following day the dog appeared to be weak, but he had an uneventful, uncomplicated recovery.

Electrocardiographic changes. Electrocardiographic recordings have been made of only a small number of dogs. As a rule the electrocardiogram changed little when the venae cavae were occluded and the animal was dependent upon the machine with its relatively small blood flow (Figs. 14A and 15A). However, intraventricular block or ventricular tachycardia occurred when stay sutures were placed in the ventricle, and especially when the interventricular septum was cut. The duration of the QRS complex decreased before the end of the procedure. In the two dogs that had electrocardiograms after one week, there was a striking return toward normal (Figs. 14B, 15B).

Ventricular fibrillation. Ventricular fibrillation has occurred only three times in 125 experiments. Cardiac massage is not necessary during artificial circulation. The heart of one dog (no. 61) fibrillated after it had been closed and the machine had been stopped. The machine was started again for eight minutes before a defibrillator was available. The heart of a second dog (no. 106) began to fibrillate 30 minutes after completion of the cardiac operation. The cannulae still were in place and he was reconnected to the machine. The heart of the

third dog (no. 113) started to fibrillate when the chest was opened. The dog quickly was connected to the artificial heart-lung. Ventriculotomy was performed and the heart was defibrillated. All three hearts could be difibrillated, and normal cardiac action and blood pressure were restored, although later we lost the dogs. The last dog died two days after the operation from atelectasis. Fibrillation also has occurred, as will be discussed later, in dogs treated with elective potassium arrest; they recovered.

Summary

Artificial heart-lung machines operate on the principle of taking blood from the venae cavae, oxygenating it and returning it to the aorta so that the heart is bypassed. The artificial lungs described here oxygenate blood while it flows through polyethylene tubing. Each unit has an oxygenating area of 14,000 sq. cm., holds 500 ml. of blood, and will oxygenate 75 ml. of blood per minute. This is enough to maintain a 2-kg. dog or patient, using the "low-flow" principle (35 ml. per kg. per minute). The lung units are cheap, disposable, and simple enough to be mass-produced.* As many as ten units can be used in parallel.

The artificial heart-lung circuit uses a third pump (Miller, Gibbon, and Gibbon[5]) so that it has a constant blood volume. The pumps are commercially available Sigmamotors. The tubing, filters, and manifold are disposable.* The apparatus is such that the subjects require only 0.8 mg. of heparin per kg. of body weight; each 500 ml. of priming (donor) blood is taken into a siliconized bottle containing 12 mg. of heparin in 30 ml. of diluent.*

Experience in about 140 experiments in dogs is reviewed. Anesthesia was light and blood loss was fully replaced. Oxygenation was more than 90 per cent, even when the venous inflow was highly unsaturated. Hemolysis was negligible. Metabolic acidosis was countered, first by hyperventilation and secondly by operative and postoperative infusions of sodium bicarbonate (4.5 mEq. per kg. of body weight each). Serum sodium increased within the normal range and serum potassium was not changed.

Bleeding problems were largely overcome. Transient disturbances of clotting mechanisms during the run, quickly reverted to normal. 'Heparin rebound' was recognized by protamine titration. It was corrected, and later prevented by repeated doses or infusions of protamine sulfate.

Arterial pressure ranged from 25 to 50 mm. Hg during occlusion of the venae cavae and extracorporeal circulation, at 35 ml. per kg. per minute; it returned to 100 mm. Hg within 5 minutes after release of the venae cavae in most successful experiments. Postoperative myocardial failure was best treated by reconnecting the subject to the artificial heart-lung, without tying of the venae cavae. This was done in 13 dogs.

Artificial circulation at small flow rates elicited only minor electrocardiographic changes, although severe changes ensued on cutting into the myocar-

* *Baxter Laboratories, Morton Grove, Illinois.*

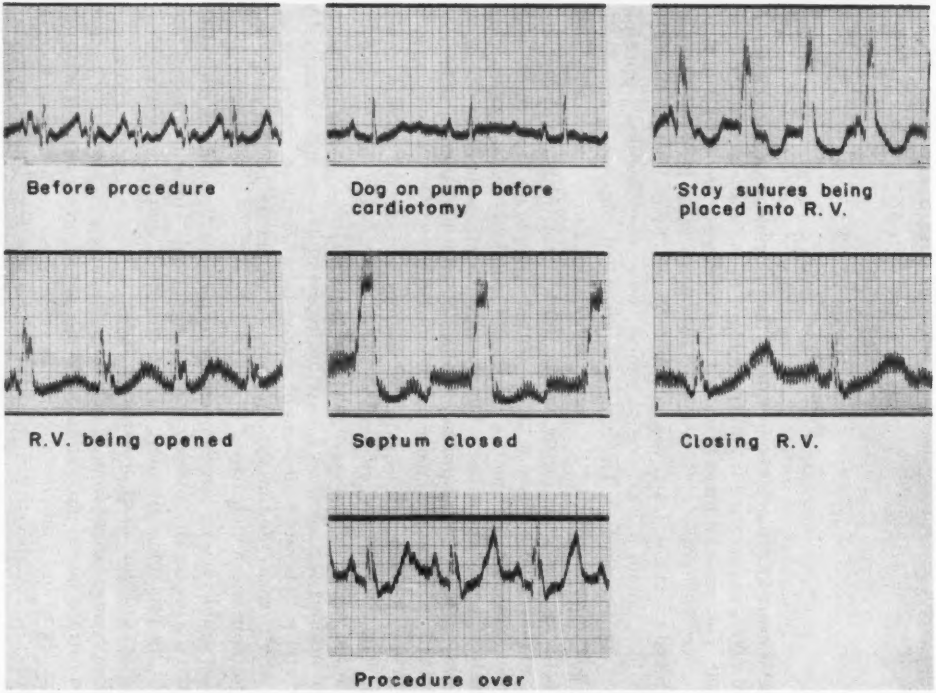

Fig. 14A. Recording at 50 mm./sec. *Before procedure. Dog on pump before cardiotomy.* P-R has increased from 0.09 sec. to 0.14 sec. and the T wave has become upright. *Stay sutures being placed into right ventricle.* Ventricular tachycardia: auricular rate *125*, ventricular rate *187*. *Right ventricle being opened.* Ventricular tachycardia. *Septum closed.* Decrease in ventricular rate to 100/min. *Closing right ventricle.* Sinus rhythm with QRS duration of 0.12 sec. *Procedure over.* Sinus rhythm with QRS of 0.10 sec.

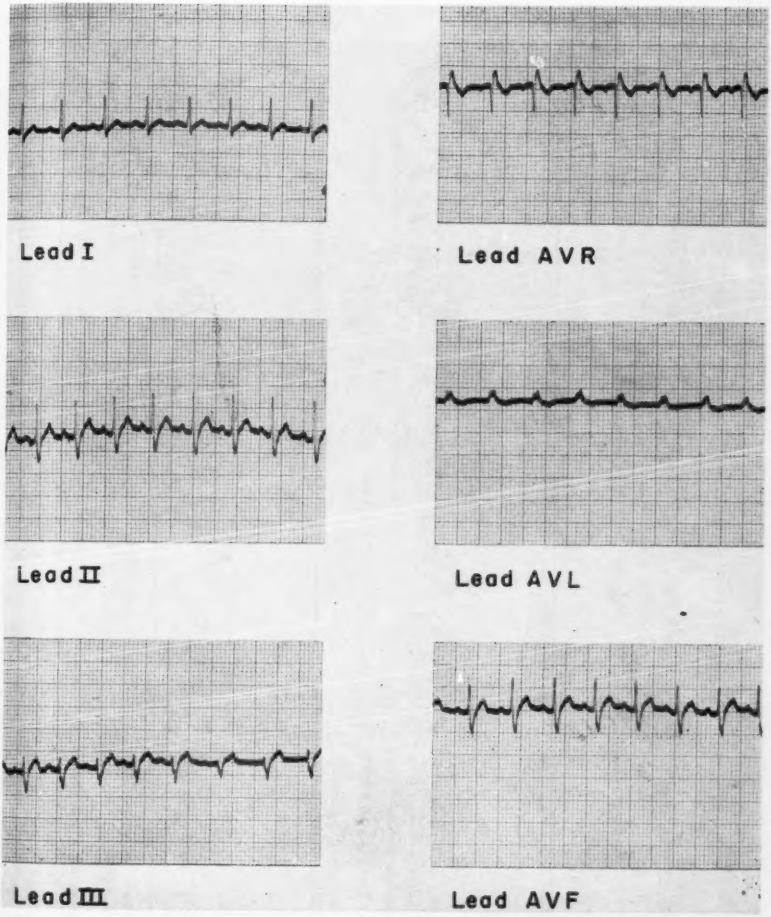

Fig. 14B. Recording at 25 mm./sec. P-R interval is the same as that preoperatively. The QRS duration is 0.08 sec. and the configuration is consistent with incomplete right bundle branch block. (*J. Mignault, M.D.*, and *W. L. Proudfit, M.D.*)

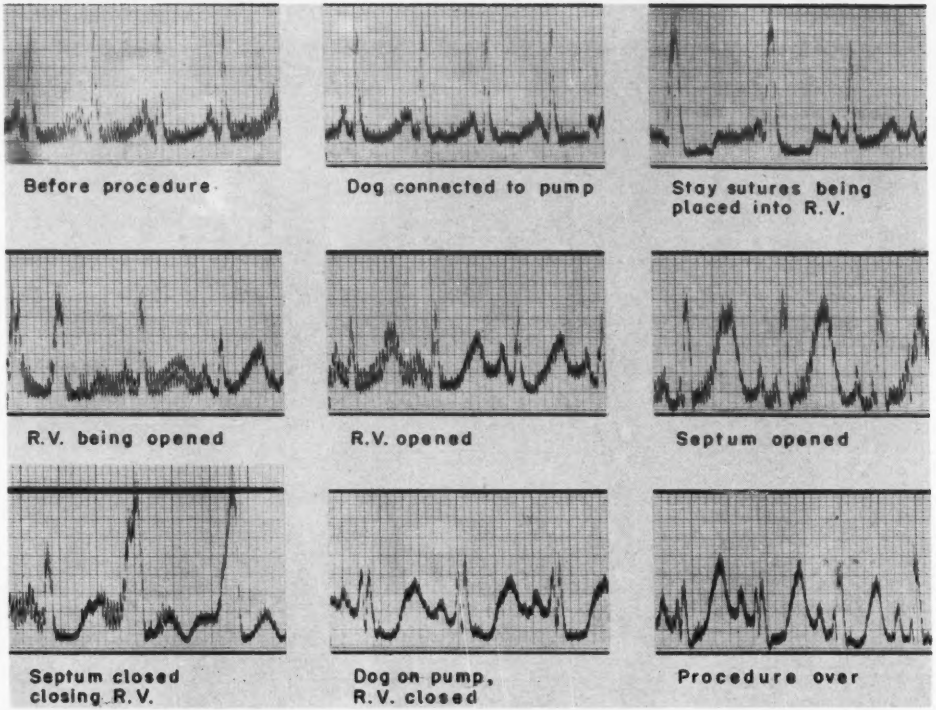

Fig. 15A. Recording at 50 mm./sec. *Before procedure.* QRS duration 0.06 sec. *Dog connected to pump.* No change from before procedure. *Stay sutures being placed into right ventricle.* QRS duration 0.08 sec. *Right ventricle being opened.* Ventricular premature contractions. T wave much higher in the normal beat. *Right ventricle opened.* Similar to previous ECG. *Septum opened.* QRS duration increased to 0.10 sec. and T waves still higher. *Septum closed, closing right ventricle.* Sagging of S-T segment and two ventricular premature contractions. *Dog on pump, right ventricle closed.* Similar to previous ECG, but T waves higher and rhythm regular. *Procedure over.* Similar to second ECG (made when

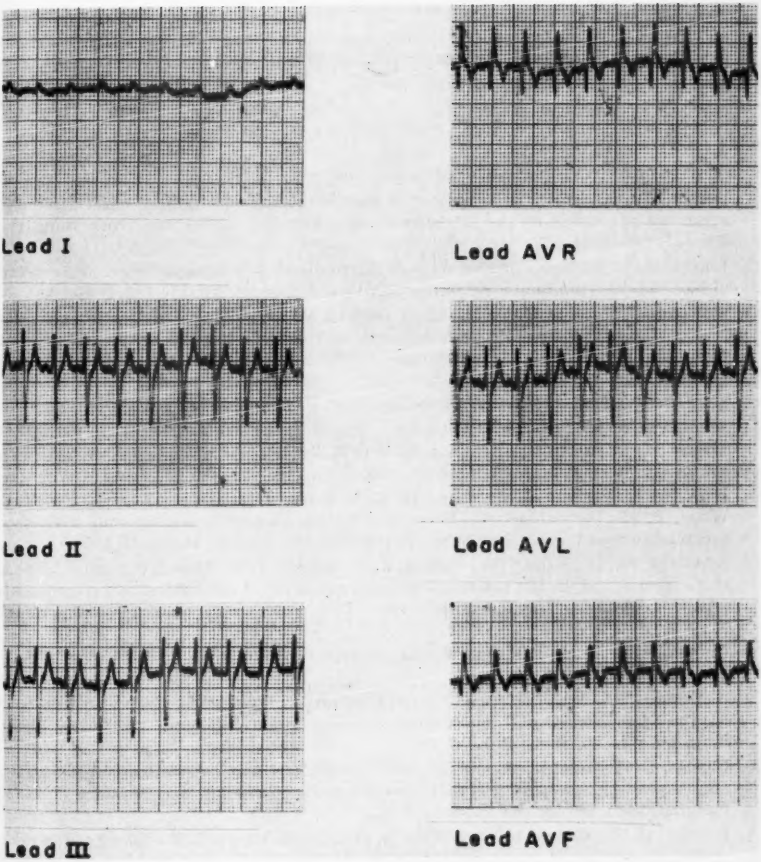

Fig. 15B. Recording at 25 mm./sec. QRS duration 0.08 sec. The configuration is consistent with incomplete right bundle branch block. T wave is inverted in lead 1.

dium. Most of these had disappeared at the end of a week. Ventricular fibrillation occurred only three times in 125 experiments. Defibrillation during the artificial circulation was easy.

Acknowledgment

We wish to acknowledge the excellent assistance of our technicians, Mr. Janis Eglajs and Miss Rose Litturi.

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ELECTIVE CARDIAC ARREST BY THE MELROSE TECHNIC

Potassium Asystole for Experimental Cardiac Surgery

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INTRACARDIAC operations would be more easily performed if the heart could be arrested and restarted at will, and if the coronary blood flow could be stopped without damage to the myocardium during the period of arrest. Visualization would be excellent in the quiescent and dry heart, suturing would be much simpler, and air embolism could not occur. This objective has now been achieved in England through the efforts of Melrose, Dryer, Bentall, and Baker.[1] The basic physiological observation was made by Ringer[2] in 1883. Hooker[3] in 1929 suggested that potassium chloride could be used to stop the heart when it is in a state of ventricular fibrillation, and he recommended using calcium chloride to restart the heart beat. Montgomery, Prevedel, and Swan[4] used a similar technic to reverse fibrillation in hypothermic patients. In our experiments with dogs, we followed closely the technic of Melrose and associates in which diastolic asystole is induced with potassium citrate, and we have been able to confirm their results.

Technic

First, the dog is connected to the heart-lung machine, as described in the preceding article. While the machine is pumping oxygenated blood at a flow rate of 35 ml. per kg. of body weight per minute, the caval and the azygos veins

* *Fellow.*

This work was supported by a grant to Doctor Kolff from the Cleveland Area Heart Society.

are closed off. Then the aorta is cross-clamped with a ductus clamp 2 or 3 cm. above the heart. In dogs weighing up to 15 kg., 2 ml. of a 25 per cent solution of potassium citrate (= ½ gm. = 4.5 mEq.) is diluted to 20 ml. by aspiration of blood into a syringe. A 22-gauge cannula is inserted into the trunk of the aorta proximal to the ductus clamp and the mixture is injected rather quickly until the heart stops beating, usually within 30 seconds. Eight or twelve cubic centimeters of the mixture often is enough (in adult human patients Melrose recommends 1 gm. of potassium citrate in 50 ml. of blood). The potassium ion stops the heart in diastole and the citrate probably potentiates the effect by reducing the proportion of ionized calcium in the blood.

During cardiac arrest the heart has a low oxygen requirement, consequently occlusion of the aorta and cessation of the coronary flow have no ill effect on it, and the dry heart may be cut, repaired, and sutured. After completion of the intracardiac operation the clamp on the aorta is released. A stream of blood immediately gushes from the sinus venosus and the thebesian veins; it is at first dark in color but soon becomes bright red, and quickly fills the right side of the heart. The first heart beat sometimes comes within 15 seconds. Melrose warns against the use of calcium in attempts to restore normal rhythm, because it tends to stimulate contraction before adequate oxygenation has been attained and may precipitate ventricular fibrillation. Flushing out of the coronary vessels with oxygenated blood from the artificial heart at once washes out excess potassium and at the same time provides oxygenation.

The right ventricle is closed only after an adequate heart beat has been restored. In the meantime the unusually large amount of coronary blood flows out freely; this avoids undue stretching of the muscle fibers, and disposes of potassium-loaded blood. If the heart were prematurely closed the potassium might re-enter the coronary arteries via the lesser circulation on the left side of the heart.

Our technic (above) requires that this and all lost blood be promptly replaced. After three minutes the heart beat usually is strong and regular and the heart may be closed. The venae cavae are released, first the superior, then the inferior. The puncture hole in the aorta sometimes causes troublesome bleeding in heparinized animals.

Results

In 10 dogs the heart was arrested by potassium citrate for periods of ½ to 23 minutes. Normal rhythm was restored in all. In one dog the heart had to be massaged after release of the venae cavae to avoid overdistention. Ventricular fibrillation occurred in one dog (experiment no. 135) so that the procedure of potassium asystole was repeated; the heart then resumed a normal rhythm and the dog recovered.

The average interval between releasing of the clamp on the aorta and resumption of cardiac action was 37 seconds. Of the 10 dogs, five recovered

completely. One dog died the night after operation; no anatomical cause for its death could be found, but it was concluded that the animal probably had not been adequately transfused. Four dogs died later from causes not related to the potassium asystole—atelectasis, empyema, pleural effusion. The last three dogs of the series were pups. It is well known that lungs of pups are difficult to handle and are prone to damage and infection. The three seemed to be in perfect health the day after operation.

Changes in serum potassium. By the above technic, most of the potassium injected into the root of the aorta is flushed out of the coronary circulation and drained from the right ventricle before the heart is closed. This is shown by the pre- and post-arrest concentrations of serum potassium listed in Table 6 of the preceding article. Even if the potassium were to be retained, the rise in serum potassium would not be dangerous, since if the 4.5 mEq. injected were diluted only in extracellular fluid—rather than total body water as is probably the case—the rise in serum potassium would be less than 1 mEq. per liter. However, repetition of potassium arrest without removal of the potassium-laden blood, i.e., with the heart closed, could be dangerous.

Electrocardiographic changes. These are demonstrated in Figures 1 and 2. The electrocardiogram sometimes showed continued electrical activity when the heart was apparently motionless; sometimes the auricles continued to beat after the ventricles had stopped. The first beats after release of the clamp usually showed distorted patterns, and auriculoventricular, intraventricular or bundle branch block were common findings. However, these changes were transient when the conductive system was not damaged by the incision.

Summary and Conclusions

Experimental cardiac asystole was elicited in dogs by the technic of Melrose and associates. Our data fully confirm their observations and show that elective cardiac arrest with potassium citrate greatly facilitates intracardiac operations, when used in conjuction with the artificial heart-lung apparatus with disposable membrane oxygenator described in the previous article.

The procedure was to connect the dog to the heart-lung apparatus, clamp the aorta and inject potassium citrate into the root of the aorta. The injection consisted of a mixture of 2 ml. of 25 per cent potassium citrate in 18 ml. of blood, of which 4 to 20 ml. were required to induce cardiac arrest. The average interval required for the heart to start beating after removal of the aortic clamp was 37 seconds. Ventricular fibrillation occurred in one of the 10 dogs, but repetition of the procedure (potassium arrest and flushing of the coronary circulation) established normal rhythm. In some experiments, the heart distended after release of the aortic clamp, because of residual potassium effect, anoxia or of the extensive myocardial wound. This distention disappeared within 3 to 15 minutes, especially when the animal's circulation was supported by the artificial heart-lung apparatus.

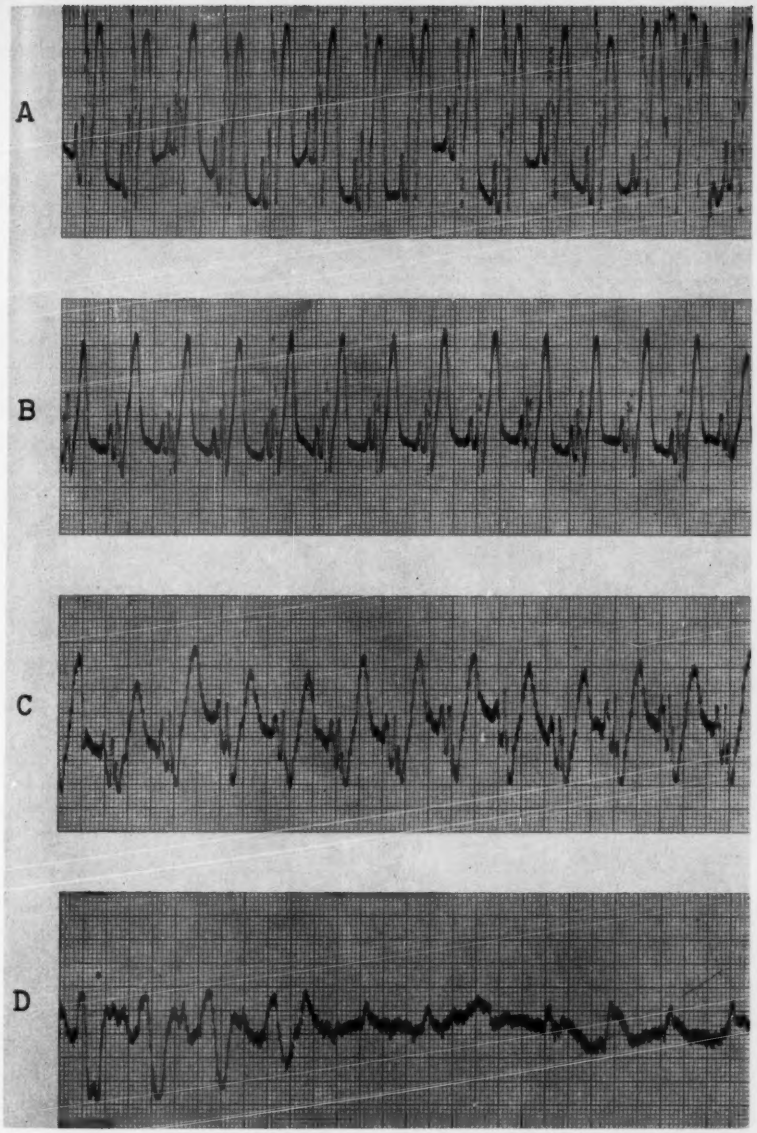

Fig. 1. Serial electrocardiograms (lead 2) obtained from a dog during induction of cardiac arrest with potassium citrate.

A. Normal sinus rhythm before pump oxygenator was started.

B. Thirty seconds after occlusion of venae cavae. Voltage of QRS complexes is reduced. A.V. conduction is unchanged.

C. Thirty seconds after clamping of the ascending aorta above the coronary orifices and infusion of potassium citrate into aorta below the clamp. Prolongation of intraventricular conduction to 0.12 seconds. A.V. conduction is unchanged.

D. Forty-five seconds after potassium infusion. There is prolongation of P-R interval and marked widening of QRS complexes, progressing suddenly to ventricular standstill. Broad atypical P waves continue to occur for a few more seconds. A.V. conduction is blocked.

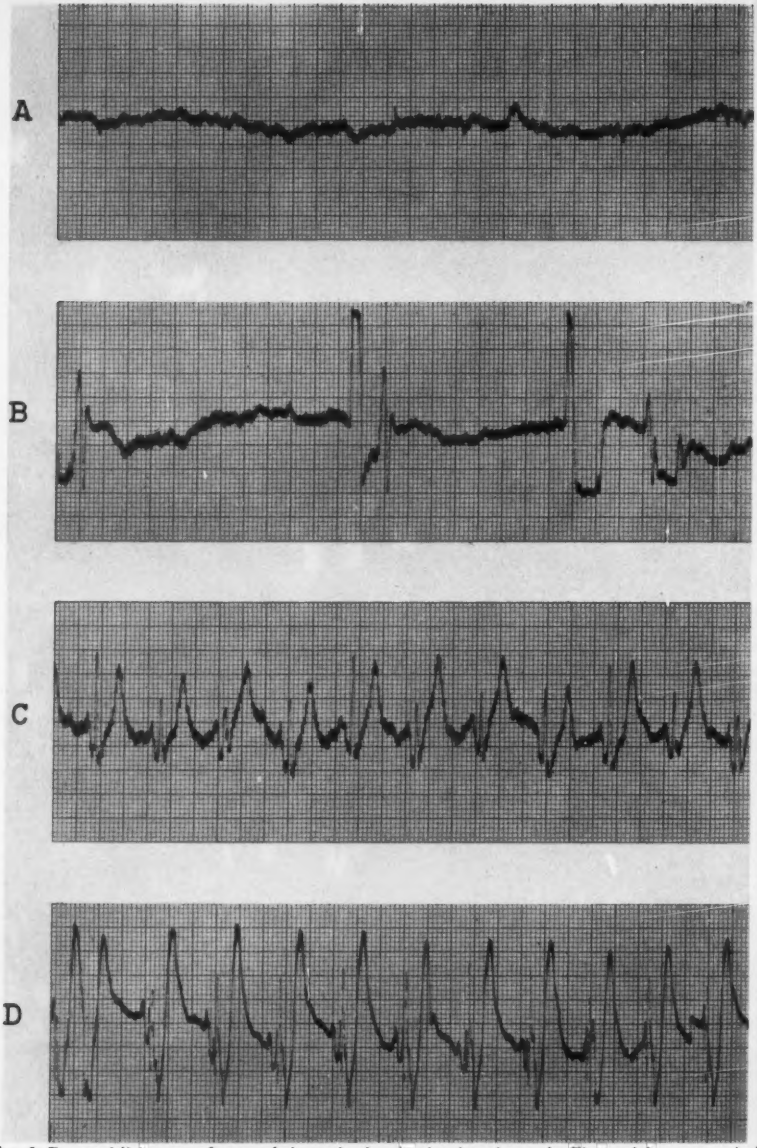

Fig. 2. Re-establishment of normal sinus rhythm in the dog shown in Figure 1 by removal of the aortic clamp, allowing perfusion of the coronary arteries with blood from the pump oxygenator. The time required was longer than usual because of an unusually traumatic intracardiac procedure in this instance.

A. Aortic clamp removed 24 minutes after cardiac arrest had been induced.

B. Coupled ventricular beats from two separate foci occurring three minutes after re-establishment of coronary artery perfusion. A.V. conduction has not yet been established.

C. Six minutes after **B**, A.V. conduction has been re-established. Intraventricular conduction has shortened. Ectopic ventricular beats have disappeared.

D. Twenty-seven minutes after the aortic clamp had been released the pump oxygenator was disconnected and an effective mechanical heart beat had been re-established. A.V. conduction is not prolonged. Intraventricular conduction is prolonged, due to incision of a large part of the interventricular septum and its surgical closure.

Experiment No.	Weight in kg.	Amount of K mixture in cc.	Duration of arrest, in min.	Type of operation	Serious arrhythmias	Measures taken to restore normal heart beat	Time interval between release of clamp on aorta and resumption of cardiac action	Comment
126	8.5	6	½ min.	Ventriculotomy	—	—	30 sec.	Died—3 days postop. atelectasis
127	7.7	10	10 min.	Interventricular septal defect	—	—	75 sec.	Recovered
128	6.0	20	5 min.	Interventricular septal defect	—	—	—	Recovered
130	13.2	15	13 min.	Longitudinal split of sternum; ventriculotomy	—	—	15 sec.	Died—8 days postop. empyema
132	10.7	—	22 min.	Auriculotomy and ventriculotomy	—	—	60 sec.	Recovered
133	10.3	—	23 min.	Ventriculotomy	—	Assisted by massage	35 sec.	Died—same night; inadequately transfused
135†	9.0	8	20 min.	Ventriculotomy	Ventricular fibrillation	Heart rearrested with K citrate	20 sec.	Recovered
137 (pup)	4.0	2	15 min.	Ventriculotomy	Transient block	—	42 sec.	Recovered
138 (pup)	3.1	4	15 min.	Ventriculotomy	Transient block	Isopropylarterenol 0.025 mg.	30 sec.	Died—4 days postop. pleural effusion
139 (pup)	3.7	4	15 min.	Ventriculotomy	—	—	27 sec.	Died—3 days postop. pleural effusion

† *After the heart had been arrested for twenty minutes and the aortic clamp had been removed, a few beats occurred, after which ventricular fibrillation set in. The heart was allowed to fibrillate for a few minutes with the heart-lung machine going. Then the aorta was clamped again and the heart was arrested again with potassium citrate. Thirty seconds after the clamp had been removed, normal pulsations began. Eleven minutes after the heart had been rearrested the heart beat was strong and regular. The heart-lung machine was used in this case for a period of 46 minutes. The dog recovered.*

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ELECTIVE CARDIAC ARREST IN OPEN-HEART SURGERY

Report of Three Cases

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IN 1954, Warden, Cohen, Read, and Lillehei[1] reported their initial experience in open-heart surgery with cross-circulation technics. Their imaginative approach and experience have given impetus to the solving of the most formidable problem in cardiac surgery. In succession, the principle of cross circulation using compatible donors, the utilization of the dog-lung preparation, and finally the perfection of the bubble-type oxygenator have introduced the era of open-heart surgery. Their work has given promise that safer and more economical methods will evolve for performing direct-vision surgery within the living heart.

Open-heart surgery requires occlusion of the venous systemic return to the heart with detour of the unsaturated blood to an oxygenator that will return blood through a major artery, usually the subclavian (Fig. 1). This bypassing procedure permits satisfactory perfusion of vital organs with a reduced flow of blood employing the "azygos flow principle."[2] This technic permits open-heart surgery via auricle or ventricle, but it does not offer a dry operating field. Although no blood returns via the venae cavae, there is a significant flow through the coronary circulation, emptying by way of the coronary sinus and the thebesian veins into the heart. In addition there may be partial aortic valvular incompetence with retrograde flow through a septal defect, and there may be a significant collateral circulation emptying into the left side of the heart, the latter in those cases where there is obstruction of the right ventricular outflow (e.g. tetralogy of Fallot). Since these channels may permit a considerable loss of blood after ventriculotomy, the total loss may amount to several liters for the time required to perform the intracardiac procedure. The handicaps

This work was supported by a grant to Doctor Kolff from the Cleveland Area Heart Society.

imposed by excessive blood loss are obvious. These are compounded by the impaired visualization of the surgical field and the constant distraction that it affords. This anticipated loss of blood makes a large reserve of blood mandatory.

The ideal method of open-heart surgery is that which affords a dry field and a motionless heart. Lillehei and his group[1] have employed temporary aortic occlusion by tourniquet to reduce for very brief intervals the volume of blood returned from the coronary vessels. However, they pointed out that this method must be used with caution, because it may result in dangerous myocardial

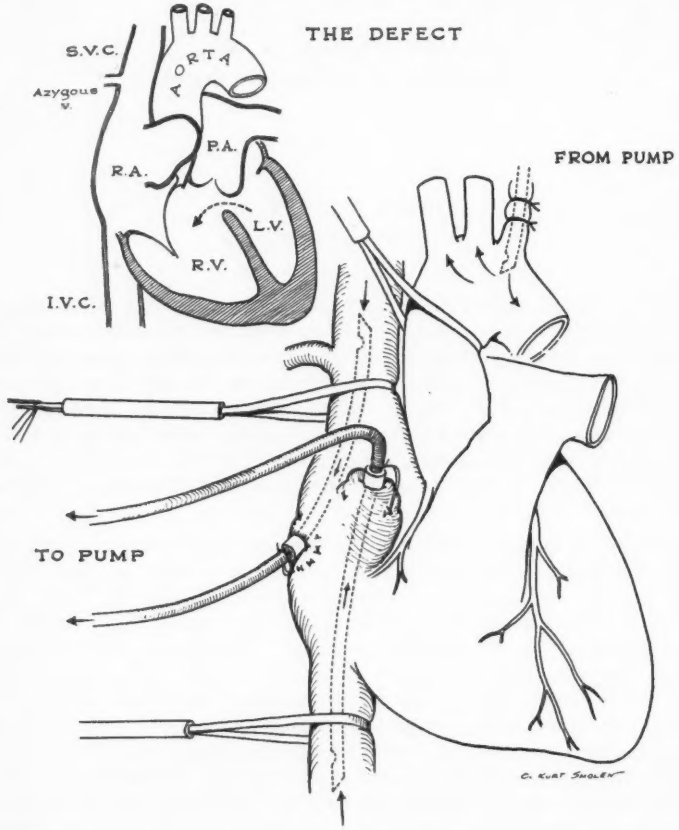

Fig. 1. Schema demonstrating the usual pattern of cannulation employed in operations with artificial maintenance of circulation. Thirty-five ml. per kg. per minute of the systemic venous return is diverted to the oxygenator by intracaval catheters. Blood returning from the oxygenator enters the aortic arch by way of a subclavian artery. This return flow of oxygenated blood perfuses the coronary arterial system, as well as the brain and other vital organs.

ischemia. Experience in the laboratory has shown that, as such, aortic occlusion provides a dry field with excellent intracardiac visualization, but that aortic occlusion while the heart is beating may cause dangerous myocardial ischemia. Since the open heart continues to beat actively during the bypassing procedure, it is logical to presume that the myocardium continues to demand oxygenated blood, even though the cardiac output is very small.

As indicated in the preceding report by Kolff and associates, it was our belief that controlled cardiac arrest would offer the ideal adjunct to open-heart surgery. Laboratory application of the method suggested by Melrose and associates[3] showed that it was a simple matter to arrest the beating heart in a healthy animal, perform an open-heart procedure, and re-establish a normal rhythm within a comparatively short time. In brief, this method consists of applying the usual technics to bypass the beating heart with a heart-lung machine, and then of injecting a potassium citrate—blood mixture into the occluded aorta immediately above the coronary ostia (Fig. 2). We use 2 cc. of a 25 per cent solution of potassium citrate mixed with 18 cc. of heparinized blood. The heparinized, oxygenated blood is taken from the pump reservoir. This simple procedure results in prompt asystole and allows direct visualization within the chambers under ideal surgical conditions: there is no blood flow and the field is both dry and motionless. This elective cardiac arrest can be terminated at will by removing the aortic occluding clamp and permitting arterial blood to perfuse the heart and to remove the potassium citrate solution. Within a matter of minutes the heart resumes a progressively stronger beat until a normal sinus rhythm has been established. Cardiac massage or stimulation has not been necessary to re-establish heart beat. In dogs this method can be safely employed for periods of 15 to 20 minutes without producing the unfavorable sequelae of myocardial ischemia. It seems logical to assume that the healthy human myocardium at complete rest can tolerate anoxia for prolonged periods of time, in contrast to the myocardium that is doing work. On the basis of these experimental observations, we decided to use elective cardiac arrest by potassium citrate perfusion as an adjunct in open-heart surgery.

Report of Cases

Case 1. A 17-month-old child weighing 22 pounds, was admitted to the Hospital for surgical treatment of a large interventricular septal defect on February 13, 1956.

Past history. The diagnosis had been made during a previous hospitalization (May 27, 1955). The physiologic data obtained from catheterization studies performed at that time (F.M.S.) are presented in Table 1.

Present illness. The child had no signs of congestive failure. There had been recent improvement in functional status, suggesting further disease of the pulmonary artery with decrease in the left-to-right shunt.

Laboratory studies. The electrocardiogram showed sinus tachycardia with right ventricular hypertrophy. The hemoglobin content was 11.4 gm. per hundred milliliters;

red cell volume 39 ml. per hundred milliliters; serum sodium 145, serum potassium 5.1, CO_2-combining power 17.6, and plasma chloride 102 mEq. per liter; blood-urea content 36 mg. per hundred milliliters; and blood pH 7.27.

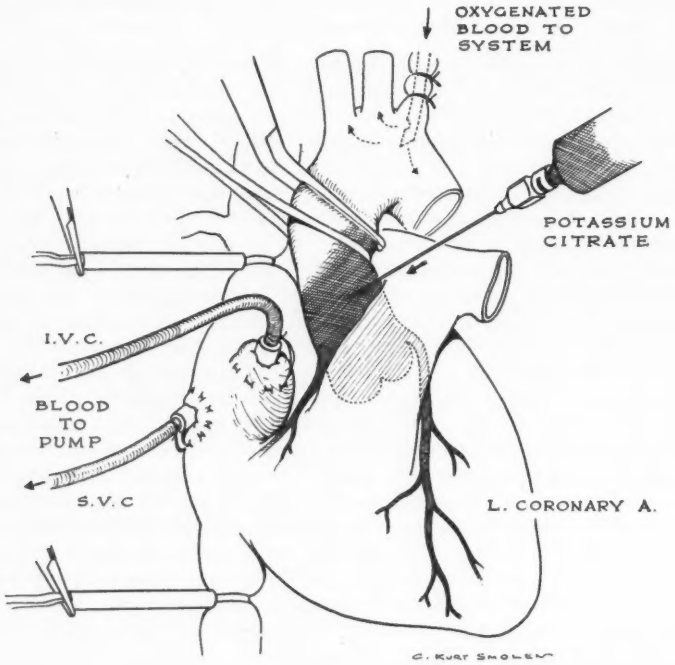

Fig. 2. Technic of elective cardiac arrest by coronary perfusion with a potassium citrate–blood mixture. The venae cavae are occluded by umbilical tapes and the heart is bypassed with the extracorporeal pump-oxygenator. The aorta has been occluded midway between the aortic valve and the innominate artery. The potassium citrate–blood mixture is indicated as being injected directly into the occluded aortic segment and perfusing the coronary bed. Less than 2 cc. of a 25 per cent solution of potassium citrate mixed with 18 cc. of oxygenated heparinized blood usually is necessary to induce arrest in a child's heart. The induced arrest is associated with myocardial paralysis. The heart appears to dilate as it becomes flaccid. Actually the dilatation is apparent rather than real, because of complete relaxation of the muscle fibers.

Operation. On February 17, 1956, open-heart surgery was performed under endotracheal anesthesia. A sternal transecting approach was used to open both pleural spaces. Artificial maintenance of circulation was established by cannulating both caval veins and the left subclavian artery. The ascending aorta was mobilized by sharp dissection and

elevated by umbilical tape. When these preparations had been completed, the superior and inferior caval veins were occluded and the venous return to the right side of the heart was bypassed to the Kolff oxygenator (Fig. 2). The heart was permitted to empty by beating for approximately 30 seconds and then the aorta was occluded at a point approximately 2 cm. distal to the aortic valves. A solution of potassium citrate (2 cc. of 25 per cent potassium citrate) in 20 cc. of heparinized blood was then injected directly into the aorta proximal to the occluding clamp. This induced cardiac arrest within one minute.

The flaccid right ventricle was then opened by a long incision. The blood was aspirated from it and the motionless surgical field was clearly visible and easily examined. The high septal defect was identified and four interrupted silk sutures were carefully placed to approximate its edges. The inspection and closure of the septal defect required approximately 10 minutes. After closure of the septal defect, the occluding clamp was removed from the aorta, the coronary circulation promptly resumed, and closure of the ventricular incision was begun. Before the closure was completed, the heart resumed a vigorous beat with sinus rhythm. After a short trial period, first with and then without support by the heart-lung machine, the heart action was considered adequate, and the chest incision was closed in the usual manner with suction drainage of 20 cm. of water to each pleural cavity.

Postoperative course. During the immediately postoperative period, care was taken to maintain normal body temperature and blood volume. Convalescence was satisfactory, and the child was discharged on March 3, 1956, 15 days after operation.

Table 1.—*Findings on catheterization studies (Case 1)*

Sample No. and location	Pressure (mm. Hg)	Oxygen content Volume %	
1. Superior vena cava	—	7.6	
			Av. 8.0 vol. %
2. Inferior vena cava	—	8.4	
3. Right auricle, high	2.0	7.6	
			Av. 7.8 vol. %
4. Right auricle, low	2.0	8.0	
5. Right ventricle, midzone	55/3	10.4	
			Av. 10.5 vol. %
6. Right ventricle, outflow tract	55/2	10.6	
7. Left main pulmonary artery	54/21	10.4	
			Av. 10.45 vol. %
8. Main pulmonary artery at bifurcation	47/20	10.5	
9. Femoral artery	98/55	11.3	(84% capacity)
Oxygen capacity		13.6	(100% capacity)
	Chest thickness, 10 cm. 0 pressure, 5 cm. above back		

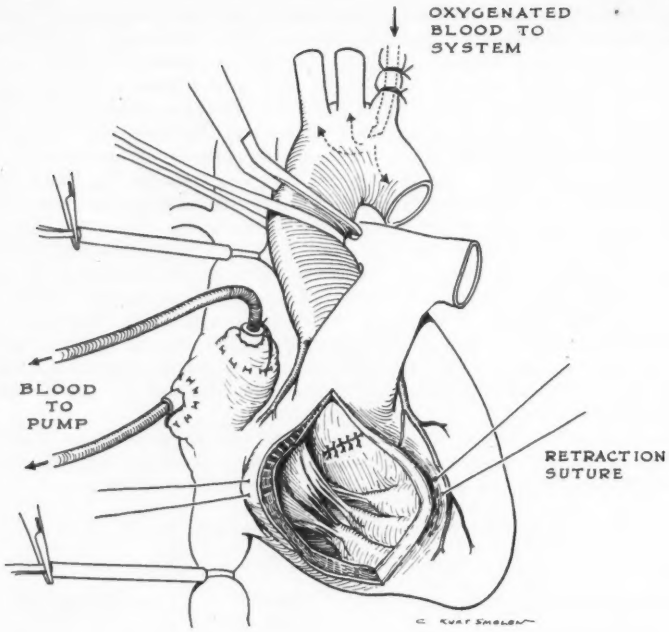

Fig. 3. Visualization of the operative field in closure of a high interventricular septal defect. A long incision is made in the anterior wall of the right ventricle, and excellent exposure is obtained by retracting sutures. The blood loss is restricted to that present in the right auricle and ventricle at the time of arrest. Release of the occluding clamp allows prompt coronary perfusion by the high pressure within the aortic arch. This washes residual excess potassium out of the coronary bed, so that the heart spontaneously resumes its normal beat.

Case 2. A 4-year-old child weighing 29 pounds was admitted to the Hospital on February 26, 1956.

Past history. Catheterization studies (F.M.S.) during a previous hospitalization on January 25, 1955, had revealed a small intra-atrial septal defect and a large left-to-right shunt at the ventricular level.

Present illness. Combined catheterization and cardioangiographic studies were performed on February 28, 1956 (Table 2), confirming the diagnosis of a high interventricular septal defect.

Laboratory studies. The electrocardiogram demonstrated sinus tachycardia and right ventricular hypertrophy. The hemoglobin content was 11.2 gm. per hundred milliliters, and the red cell volume was 40 per cent. The blood-urea content was 33 mg. per hundred milliliters, serum sodium 140, serum potassium 4, and plasma chlorides 110 mEq. per liter.

Table 2.—*Findings on catheterization studies (Case 2)*

Sample No. and location	Pressure (mm. Hg)	Oxygen content Volume %	
1. Superior vena cava	—	11.3	
			Av. 11.4 vol. %
2. Inferior vena cava	—	11.5	
3. Right atrium, high	1.0	10.9	
			Av. 11.1 vol. %
4. Right atrium, low	1.0	11.3	
5. Right ventricle, outflow tract	85/6	15.1	
			Av. 14.3 vol. %
6. Right ventricle, midzone	85/6	13.5	
7. Left atrium	2.0	16.1	
8. Pulmonary vein	3.0	16.5	
9. Left ventricle	105/6	16.5	
10. Femoral artery	105/57	16.5	(90% capacity)
Oxygen capacity		18.3	(100% capacity)
	Chest thickness, 14 cm. 0 pressure, 7 cm. above back		

Operation. On March 12, 1956, open-heart surgery was performed under endotracheal anesthesia. The surgical approach was identical to that employed in the first patient. The caval veins were occluded, connections made to the Kolff oxygenator and pump, and cardiac arrest was induced by direct injection of 16 cc. of the potassium citrate-blood mixture into the proximal aorta. The heart beat stopped within 50 seconds and the heart remained completely flaccid during the remainder of the procedure. A long incision was made in the wall of the right ventricle. Excellent exposure of the interventricular septum was obtained, and the large, high, septal defect was easily visualized. It was closed with five interrupted silk sutures. The procedure required seven and one-half minutes after induced arrest. The occluding clamp was removed during the ventricular closure. The heart resumed a progressively stronger beat within 38 seconds of return of the flow of blood, and both sinus rhythm and an effective beat were established in a short time. The cannulae were removed and the chest was closed in the conventional manner.

Postoperative course. The immediately postoperative condition was excellent. The child promptly regained consciousness; color was good and all reflexes were normal.

Blood loss was carefully measured and replaced. There was no evidence of cardiac arrhythmia at any time. Approximately 10 hours after surgery the child suddenly died after fainting while sitting up.

Autopsy revealed dilatation of the right auricle and ventricle. There was no evidence of significant bleeding. The septal defect was satisfactorily closed and there was no impairment of the right ventricular outflow tract, nor of the aortic or pulmonary valves. The reason for the sudden cessation of the heart beat was not apparent.

Case 3. A 3-year-old child weighing 32 pounds was admitted to the Hospital on March 4, 1956, for surgical treatment of a high interventricular septal defect.

Past history. Catheterization studies were performed by one of us (F.M.S.) during a previous hospital admission on June 29, 1954 (Table 3). Prior to that time the child had

Table 3. *—Findings on catheterization studies (Case 3)*

Sample No. and location	Pressure (mm. Hg)	Oxygen content Volume %		% Saturated
1. Superior vena cava	—	10.9		68.1
			Av. 11.1	
2. Inferior vena cava	—	11.3		70.6
3. Right auricle—high	1.0	10.7		66.8
			Av. 11.45	
4. Right auricle—low	1.0	12.2		76.2
5. Right ventricle, midzone	79/2	13.7		85.6
			Av. 13.85	
6. Right ventricle below pulmonary valve	76/0	14.0		87.5
7. Main pulmonary artery	76/22	14.1		88.1
			Av. 14.13	
8. Left main pulmonary artery	80/16	14.0		87.5
9. Right main pulmonary artery, proximal	60/18	14.3		89.3
10. Pulmonary vein—left middle	—	15.7		98.1
11. Left auricle	7.0	15.5		96.8
12. Right auricle (check)	—	11.1		69.3
13. Femoral artery	115/60	15.5		96.8
Oxygen capacity		16.0		100.0

had anoxic attacks. A heart murmur first had been detected at six weeks of age. During the first year of life the patient had gained weight slowly and had several bouts of pneumonitis accompanied by cough and fever.

Laboratory studies. The electrocardiogram demonstrated right ventricular hypertrophy and sinus tachycardia. The findings on all blood studies were within the normal range.

Operation. On March 15, 1956, open-heart surgery was performed under endotracheal anesthesia. The sternum was transected as described in Case 1. The left subclavian artery was cannulated for return of arterialized blood from the Kolff oxygenator; both venae cavae were then cannulated through the wall of the right ventricle. The proximal aorta was mobilized and umbilical tape placed around it to assist in occlusion. After the venae cavae had been occluded and the oxygenator and pump had begun to operate, the heart was paralyzed in diastole by injecting potassium citrate-blood mixture (17 cc.) into the proximal occluded aorta. A long incision was made in the right ventricular wall, and the right ventricle was inspected. The septal defect was lower than had been anticipated and was located with some difficulty immediately behind the septal leaflet of the tricuspid valve. It was necessary to cut one large papillary muscle to expose the defect, which was closed with five interrupted silk sutures. The transected papillary muscle was then sutured to its base. Identification and closure of the septal defect required approximately 13 minutes. The occluding clamp was removed from the aorta and the blood flow to the coronary system was restored. Twenty-five seconds later the heart beat spontaneously returned and it proceeded to a normal effective sinus rhythm. The right ventricle was open for approximately 16½ minutes. The remainder of the operative procedure was completed as usual.

Postoperative course. The immediately postoperative period was uneventful. Convalescence in the Hospital was satisfactory except for superficial bleeding from the incision approximately 24 hours after surgery. The bleeding was controlled by pressure dressings and transfusion of 50 ml. of blood. The child was discharged from the Hospital on March 29, 1956.

Summary and Conclusions

Successful extracorporeal maintenance of circulation and oxygenation using the 'small-flow' (35 ml. per kg. of body weight per minute) principle has introduced an era of open-heart surgery. As part of the search for safer and simpler methods of intracardiac surgery, controlled cardiac arrest was effected as an adjunct to the use of the artificial heart-lung. The method described in this report is based on that of the experimental work of Melrose and associates.

Elective cardiac arrest by injection of potassium citrate-blood mixture via the root of the aorta into the coronary vessels is believed to be a simple and safe procedure that offers great promise as a means of simplifying technic in open-heart procedures.

Three case reports are presented. In each case intracardiac operations were performed after cardiac arrest had been induced by coronary perfusion with potassium citrate solution. The results obtained encourage continued use of this procedure.

In each of the reported cases, the Kolff oxygenator (described in the preceding article) was employed.

Addendum

Since this paper was submitted for publication, the technic of elective cardiac arrest has been used successfully in an additional five cases.

Acknowledgments

We are especially appreciative of the assistance and advice of Donald E. Hale, M.D., Department of Anesthesiology, and John W. King, M.D., Department of Clinical Pathology.

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ATHEROSCLEROTIC COMPLICATIONS OF HYPERTENSIVE DISEASE: RELATION TO THERAPEUTIC RESPONSE AND TO SERUM PROTEIN AND TO LIPOPROTEIN CONCENTRATIONS

Preliminary Report

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THE course and prognosis of severe essential hypertension have been profoundly modified, in the past five years, by the effective use of antihypertensive drugs in patients with advancing vascular disease.[1] Favorable responses to these agents can be anticipated in a majority. Such responses include lowering of arterial pressure, stabilization or remission of, or, in some patients, actual recovery from manifest cardiac, cerebral, or renal hypertensive vascular disease.[2]

Although the mechanisms and sites of action of the available antipressor agents are varied, the common denominator of their effectiveness is the lowering of arterial pressure. This is followed by improvement of the obvious aspects of renal or cerebral arteriolosclerosis or of cardiac failure. Such remissions are clinical confirmations of the experimental finding that high blood pressure, per se, is the primary cause of arteriolar damage and cardiac strain. While hypertensive vascular disease is primarily an affliction of the *arterioles*, its association with *arterial* disease, namely, atherosclerosis, is also well recognized. The purpose of this report is to describe the beneficial effects of antihypertensive therapy on the survival of patients with advancing vascular disease and to discuss the extent to which atherosclerotic complications are affected by treatment.

Some of the many glowing reports on the use of antihypertensive drugs overlook the axiom that new solutions resolve old problems, but they inevitably create new ones. Unfortunately not all the old problems have been solved, for there still are a few patients in whom blood pressure is not controlled by the present therapeutic regimens; in these arteriolar disease continues[3]. The new problem of major and increasing concern is the occurrence of complications of atherosclerosis in treated patients, including some who respond well in terms of cardiac and arteriolar status, blood pressure, and general well-being. Some aspects of this problem have been discussed elsewhere[4,5]; and others[6] have noted "the unpleasant fact . . . that despite improvements in other respects, many patients after being restored to comfort and to living productive lives, die

unexpectedly of a stroke." But, as we shall show, strokes are only one aspect of the problem. The basic issue is that of arterial disease, namely, atherosclerosis.

Clinical material. Our report is based on a five-year survey of results of treatment of 106 hypertensive patients, nearly all of whom had been under treatment with antihypertensive drugs. Before treatment was begun, all were observed in the ward of the Research Division. There, during several weeks of study and evaluation,[7] the hypertension was categorized as malignant in 61 and as essential (nonmalignant) in 45. The severity of the hypertensive disease was scored according to a Severity Index[2,7] that covers a range from 1 (minimal hypertension) to 16. The index is the sum of the points that four panels rate on a scale from 0 to 4. The panels are (a) diastolic arterial pressure, the functional status (b) of the heart, and of the (c) cerebral, and (d) renal circulations.

Seventy per cent of the patients were between 40 and 59 years of age. In this age group, hypertension generally is more common in women than in men. The fact that two thirds of the patients were men reflects the greater severity of hypertensive disease in the male sex.

Survival and severity. Experience in this series clearly demonstrated the prognostic value of the severity index. In the group of 61 patients having malignant hypertension the mean index of severity was 9 and the mortality was 44 per cent. In the group of 45 patients having essential hypertension, the mean index of severity was 6 and the mortality was 27 per cent. Furthermore, in the 'malignant' group, mortality was 70 per cent for the subgroup having severity indexes of 10 or higher, and only 25 per cent for the subgroup having severity indexes from 6 to 9.9. Among survivors of the 'essential' group the mean index of severity was 5.4 and among those who died it was 7.3.

The cumulative survival in the 'malignant' group is graphically presented in Figure 1. This is a dramatic demonstration of the efficacy of modern methods of treatment in comparison with previous experience. In 1939, Keith, Wagener, and Barker[8] reported a four-year survival rate of 2 per cent in relatively untreated patients who had been classified as having grade IV hypertension; whereas, experience to date shows a 25 per cent four-year survival rate in our clinically comparable group. Since one fourth of the deaths in our patients were due to pulmonary fibrosis associated with the use of hexamethonium—a complication that has not occurred during the past three years—it is likely that the four-year survival rate of patients who now are beginning to receive treatment will be of the order of 40 per cent.

The causes of death in this series are listed by major subgroups in the Table, together with the incidence of nonfatal atherosclerotic complications. The high frequency (37 per cent) of renal failure as the cause of death in patients with malignant hypertension is to be expected. Most of the patients who died of renal failure had shown evidence of renal damage at the time that treatment was begun. Since a minority with initially severe renal damage have survived for several years, we believe that renal failure does not contraindicate vigorous treatment of malignant hypertension although it lessens the prospect of success and increases the difficulties. The one death from renal failure in the 'essential' group occurred in a patient who evidently had developed terminal malignant

Table.—*Causes of death, and incidence of nonfatal atherosclerotic complications (106 patients)*

Group	Cause of death	No. of patients	Nonfatal atherosclerotic complications	No. of patients
Malignant (61 patients)	Renal failure	10	Cerebrovascular accidents (among 34 survivors)	7
	Pulmonary fibrosis	7		
	Atherosclerosis	10		
	Myocardial infarct . . 5			
	Cerebral hemorrhage . 4			
	Aortic aneurysm . . . 1			
	Total	27		7
Essential (45 patients)	Renal failure	1	Cerebrovascular accident	1
	Atherosclerosis	11	Angina pectoris	2
	Myocardial infarct . . 5		(among 33 survivors)	
	Cerebral hemorrhage . 5			
	Aortic aneurysm . . . 1			
	Total	12		3
	TOTAL	39		10
	Total number of deaths resulting from atherosclerosis. . . . 21*			

**After this list had been compiled and the manuscript completed, one man in the 'malignant' group (response fair) died of dissecting aneurysm of the aorta, and another (response fair) died of cerebral hemorrhage, bringing the total number of deaths resulting from atherosclerosis to 23.*

hypertension (without the characteristic retinopathy), since at autopsy the kidneys showed typical malignant nephrosclerosis.

Atherosclerotic disease. The incidence of atherosclerotic complications, such as cerebrovascular accident, myocardial infarct, angina pectoris, and aortic aneurysm, is also shown in the Table. In this report patients who had those complications were classified as *atherosclerotic*, and the remainder of the patients, without prejudice to their presumed latent atherosclerosis, were provisionally classified as *nonatherosclerotic*.

In these terms, atherosclerosis accounted for somewhat more than half of the deaths in the entire group (Fig. 2); it was as frequent a cause of death as renal failure in the 'malignant' group and it was the cause of nearly all of the deaths in the group having essential hypertension. The dotted line in the figure suggests that atherosclerosis would have accounted for as large a proportion of deaths in the 'malignant' group if renal failure and pulmonary fibrosis had not supervened. It is probable that as more patients with malignant hypertension receive treatment before they have sustained severe renal damage, a larger proportion will survive only to die from atherosclerosis.

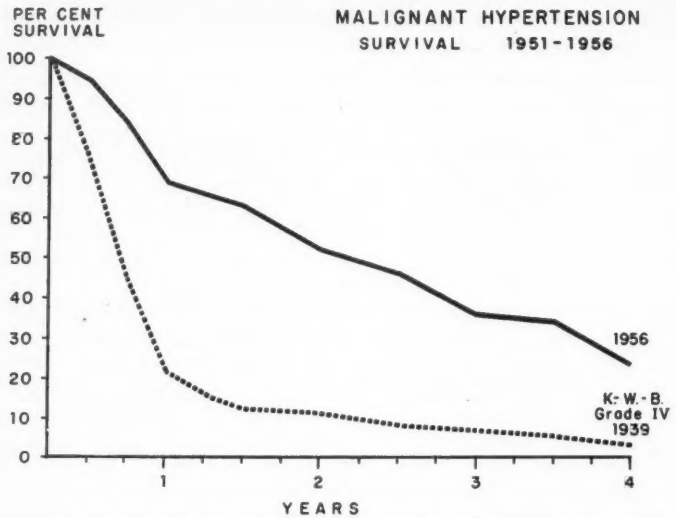

Fig. 1. Cumulative survival rates in the grade IV group of Keith, Wagener, and Barker,[8] as reported in 1939 (dotted line), and in our patients with malignant hypertension (continuous line) as of March 1956.

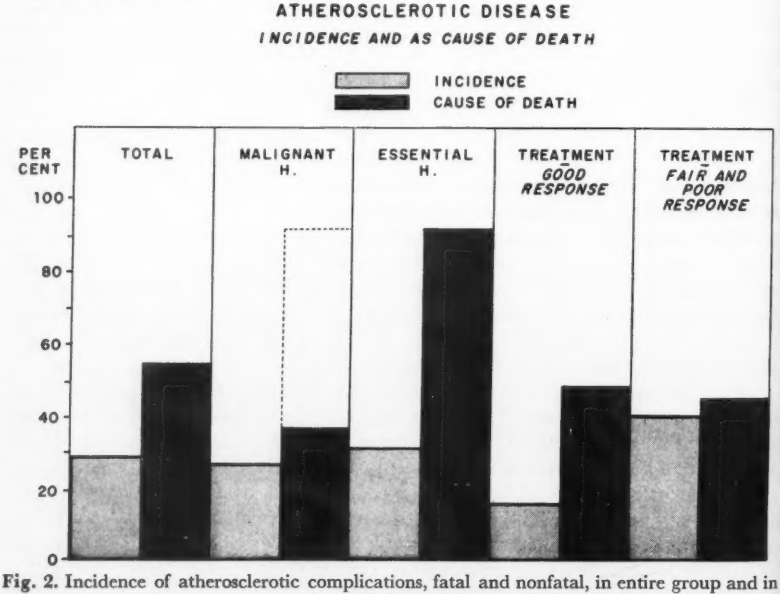

Fig. 2. Incidence of atherosclerotic complications, fatal and nonfatal, in entire group and in subgroups (shaded areas), and incidence of atherosclerotic complications as causes of death (black areas).

The patients also were classified according to an estimate of therapeutic response. The *good-response* group comprises those patients who maintained averages of resting, supine, diastolic pressures of less than 110 mm. Hg; those in the *fair-response* group had averages ranging from 110 to 120; and those in the *poor-response* group had averages of more than 120 mm. Hg. However, even the patients in the poor-response group showed at least temporary remission of the signs of malignant hypertension. For the discussion that follows, the fair- and the poor-response groups have been combined into one group (fair-poor response group).

The percentages of deaths caused by atherosclerosis were approximately equal in the two response groups. It is significant that the incidence of atherosclerotic complications, fatal or not, is much less (16 per cent, 8 of 49 patients) in those patients with good responses than it is in those with fair-poor responses (40 per cent, 23 of 57 patients). The major common characteristic of the fair-poor response group is persistence of diastolic hypertension, which indicates that in man diastolic hypertension per se contributes greatly to atherogenesis. This also is true in rabbits[9] and in dogs.[10] The corollary should be that early, effective control of diastolic hypertension is a primary means of preventing the development of atherosclerotic complications.

Serum protein and lipoprotein analyses. Serum protein concentrations were measured electrophoretically by the Longsworth modification of the method of Tiselius, and lipoprotein concentrations by the Green, Lewis, and Page[11] modification of the Gofman procedure. Serum cholesterol was determined by the method of Abell, Levy, Brodie, and Kendall.[12]* Since these data have not yet been completely analyzed, this presentation is, in part, preliminary.

Inspection disclosed no consistent abnormalities in concentrations of the electrophoretically separated serum protein fractions other than those of beta-globulin, so that data concerning this fraction were studied first. In regard to lipoproteins, current interest in the light, lipid-rich fractions of the beta-lipoproteins and in the ratio of these to the concentration of relatively dense, lipid-poor alpha-lipoproteins prompted us to select for initial review data concerning the $-S_{1.21}$ fractions 2-8 (corresponding to alpha-protein) and the fractions 40-70 (corresponding to the S_f 12-100 material in Gofman's unmodified procedure).

Figure 3 summarizes the data concerning beta-globulin and serum cholesterol. The mean normal concentration of beta-globulin by this method is 13 per cent and the upper limit of normal is about 17 per cent. Hence, the mean concentration of beta-globulin is increased in the entire hypertensive group; it is somewhat greater in the malignant than in the essential subgroup and in those who had atherosclerotic complications than in those who did not have them. Except in the good-response group, the means of concentration of serum cholesterol show some association with the averages of beta-globulin. The lipoprotein data are not shown, since the means of concentrations of the two fractions studied and of their ratios one to another are nearly the same in all the groups.

**Determinations were made with the assistance of Helen Brown, Ph.D., of the Division of Research.*

The observed differences in mean concentrations of beta-globulin and of cholesterol between the subgroups of Figure 3 are not statistically significant. However, the differences between the means may indicate trends that, in a much larger series, might prove statistically significant. This is suggested by the fact that the incidences of abnormal concentrations of cholesterol follow the trend of the means of the concentrations. Thus, the concentrations of beta-globulin were 17 per cent or more in two thirds of the entire group and in about the same proportion of each of the subgroups; concentrations of serum cholesterol were increased (greater than concentrations found in 80 per cent of normal subjects of matched age and sex) in one fourth of the entire group, in one third of the malignant, in one seventh of the essential, in one third of the atherosclerotic, and in one fifth of the nonatherosclerotic groups. Abnormal concentrations of the lipoprotein fractions were uncommon. Thus, the -$S_{1.21}$ 2-8 fraction was high in 5, and low in 14 of 77 patients; and the fraction 40-70 was high in 8, with no trend toward higher incidences in any of the subgroups. The conclusion from this is that hypercholesteremia or abnormalities of the lipoprotein fractions studied are not major determinants of atherogenesis in hypertensive disease, although study of a larger series might reveal some minor contributory influence.

Serum beta-globulin in hypertensive disease. Increased concentration of serum beta-globulin was found to be associated with the presence of hypertensive vascular disease in patients with malignant hypertension, and in dogs with experimental renal hypertension[13] (Fig. 4). More recently, this increased concentration was observed in rats made hypertensive by treatment with desoxy-

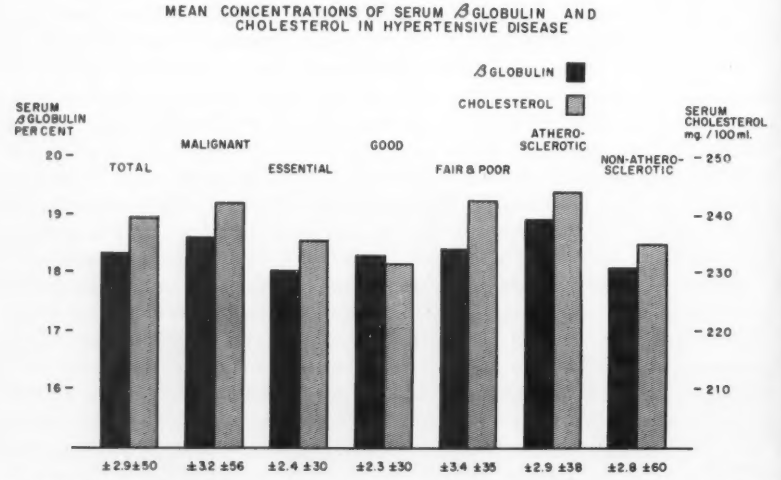

Fig. 3. Means of concentrations of serum beta-globulin (black areas) and cholesterol (shaded areas) in entire group and in subgroups. The numerals below each column indicate standard deviations of the means. Data compiled from analyses made simultaneously in 78 patients, prior to use of antihypertensive drugs.

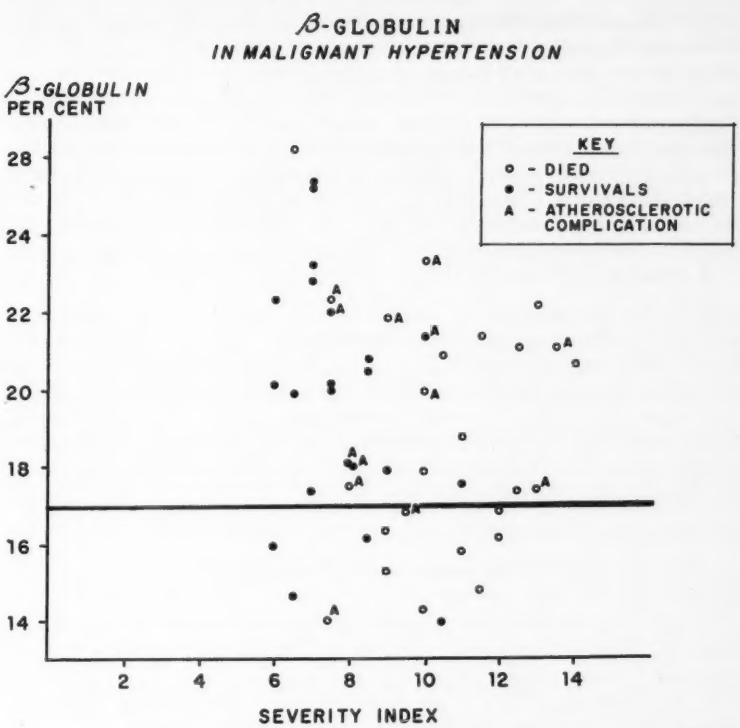

Fig. 4. Scatter of serum beta-globulin concentrations in our patients with malignant hypertension, and lack of correlation with severity indexes, mortality, and atherosclerotic disease.

corticosterone acetate (DCA) and sodium chloride; in these the abnormality was increased by injections of renin; the increased concentration did not appear in rats treated with cortisone and sodium chloride or with sodium chloride alone, but it was elicited in rats treated with cortisone and sodium chloride and then renin injection.[14] The positive correlation of increased concentration of beta-globulin with hypertensive disease was again evident in these experiments; severe vascular damage is present in rats given DCA and NaCl, and may assume a hyperacute form in rats given DCA, NaCl and renin, or in rats given cortisone, or NaCl and renin; whereas, under these conditions, neither NaCl alone nor cortisone and NaCl elicit more than minor hypertension and do not provoke lesions with the characteristics of hypertensive vascular disease.

Hence, there is clinical as well as experimental evidence of an association of increased concentration of serum beta-globulin and hypertensive vascular disease. This association is further borne out in the lowering of the concentration

of serum beta-globulin which occurs during treatment, and by the finding that the decrease is greater in patients with good responses than in those with fair or poor responses.[5] But, since the nature of the abnormality of beta-globulin is not characterized, the significance of this association is purely speculative. The data do indicate some correlation between changes in beta-globulin and changes in serum cholesterol. This, in turn, suggests that the increment in concentration of beta-globulin may be due to a cholesterol-containing lipoprotein that migrates electrophoretically as a beta-globulin. On the basis of present data, this fraction does not correspond either to the relatively dense or to the relatively light lipoprotein fractions. Further study of the available data may determine where this material is distributed in the ultracentrifugally measured fractions.

Here, for the moment, the problem rests. However, the association of increased concentrations of serum beta-globulin with hypertensive vascular disease as such and, to a minor degree, with inadequate responses to treatment and with predisposition to atherosclerotic complications, indicates that definition of the nature and mechanism of this abnormality may be of considerable value. To our knowledge, increased beta-globulinemia represents one of the few, if not the only aspect of the chemistry of the blood that can be considered an abnormal characteristic of hypertensive vascular disease.

Summary and Conclusions

1. The prognosis in severe hypertension has been greatly improved by the advent of effective antihypertensive drugs. Today, patients with malignant hypertension have a four-year survival rate of 25 per cent, as compared with about 2 per cent in 1939; it is likely that patients coming under treatment at this time will have a four-year survival rate of about 40 per cent.

2. A numerical index of the severity of hypertensive disease is useful in assessing prognosis as well as in therapeutic evaluation.

3. The present status of hypertensive disease involves two major problems. One is that of patients who are partially resistant to drug treatment. The other is that of atherosclerotic complications.

4. Atherosclerotic disease is a major cause of death and disability in patients under treatment for hypertensive disease, including some with good therapeutic responses. These complications are two to three times more common in patients whose resting diastolic pressures average 110 mm. Hg or more, than in patients with good responses (diastolic average less than 110 mm. Hg).

5. The concentration of serum beta-globulin is increased in a majority of patients with severe hypertensive disease. Concentration of serum cholesterol is increased in a minority of patients. Means of the concentrations of serum beta-globulin and cholesterol in subgroups show some correlation. Neither the relatively dense ($-S_{1.21}$ 2-8) nor the relatively light (40-70) serum lipoprotein fractions show differential changes between these malignant and essential, atherosclerotic and nonatherosclerotic subgroups of patients. From these findings it seems that abnormalities of serum cholesterol or of these serum lipoprotein

fractions are not major factors in atherogenesis in hypertensive disease.

6. Rather, the primary factor is arterial hypertension, and the prevention of atherosclerotic complications is best accomplished by prompt, effective, and persistent control of hypertensive disease.

7. Attention is directed to the association of increased concentration of serum beta-globulin with clinical and experimental hypertensive disease, the possibility that the abnormality may be due to a lipoprotein, and that this is the only abnormality of blood chemistry that seems to be characteristic of hypertensive disease.

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INTERNAL BILIARY FISTULA

Report of 18 Cases

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INTERNAL biliary fistula is an abnormal communication between a portion of the extrahepatic bilary tract and any other viscus. The fistula may result from trauma, inflammatory disease, calculi, or malignant disease of the biliary tree per se, or from traumatic, inflammatory or neoplastic disease of adjacent organs.

Our study is based on the findings in 18 patients who had internal biliary fistulas; one case of spontaneous cholecystocolic fistula is included which previously had been reported by Michels and Hoerr.[1]

Incidence

Although internal biliary fistula is an uncommon complication of chronic cholecystitis and cholelithiasis, the incidence of the lesion frequently is underestimated. In one large series[2] of patients undergoing biliary surgery at the Mayo Clinic, the incidence of internal biliary fistulas was 0.86 per cent, while in a somewhat smaller recent series here, the incidence was 0.5 per cent.

The sex ratio in the 18 patients of this report, 13 women and 5 men, approximates that which generally has been reported for the condition, and is comparable to the sex ratio for patients having cholelithiasis. The range of ages was 43 to 72 years, with an average of 57.6 years (Table 1).

Table 1.—*Age and sex distribution*

Age range (yr.)	No. of women	No. of men	Total no. of patients
40-50	3	2	5
51-60	5	2	7
61-70	2	1	3
71-80	3	0	3
TOTAL	13	5	18

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In the order of their frequency, the most common of the internal biliary fistulas are the cholecystoduodenal, cholecystocolic, and choledochoduodenal. Waggoner and LeMone,[3] who summarized 819 reported cases of internal biliary fistulas, found that 50 per cent were of the cholecystoduodenal type, 21 per cent of the cholecystocolic, 19 per cent of the choledochoduodenal, and 9 per cent of other types. In that group of 9 per cent were included those rare biliary fistulous communications with the bronchial tree, the pericardium, the portal vein, the hepatic artery, the renal pelvis, the uterus, the vagina, the bladder, the small intestine, and stomach; an ovarian cyst, an echinococcus cyst, and those between the gallbladder and the common bile duct.[2,4-9]

Bennett and Hewko[10] observed the passage of gallstones from a sinus that had been established for drainage of a right empyema. Berens, Hallenbeck, and Cain[11] reported an unusual case of a cholecystoduodenal fistula associated with a spontaneous rupture of the abdominal wall by a chronic abscess containing a gallstone. Epperson and Walters[2] refer to a case of an 87-year-old woman who had had a gallstone ileus as a result of a fistulous communication between the gallbladder and the small bowel.

In the 18 cases of biliary fistula presented here, nine fistulas were cholecystoduodenal, five were choledochoduodenal, three were cholecystocolic, and one involved a communication between the stump of the cystic duct and the first portion of the duodenum. In one case of the cholecystocolic type, three fistulous communications were identified.

Etiology and Pathogenesis

The relatively high incidence of cholecystoduodenal fistula is attributable to the normal proximity of the gallbladder and the duodenum, to the mobility of the duodenum and, in some instances, to the adherence of the duodenum to the gallbladder as a result of inflammatory disease of the gallbladder. Similarly, the frequency of cholecystocolic fistula results from the normal proximity of the gallbladder and the colon. The rarity of the cholecystocholedochal fistula probably is attributable to the fixed position of the common bile duct and the relative immobility of the gallbladder.

The majority of cases of biliary fistula are associated with chronic cholecystitis and cholelithiasis. Noskin, Strauss, and Strauss[12] estimated that in 90 per cent of the cases a gallstone is the provocative agent; in approximately 6 per cent perforating ulcer is the offending factor; and in the remaining 4 per cent the etiologic sources are carcinoma of the gallbladder or of the biliary tree, abscesses in the biliary tree, and such rarities as echinococcus cysts.

Chronic cholecystitis and cholelithiasis with an inflammatory and ulcerative process in the gallbladder wall may lead to erosion and penetration of the wall by a stone and eventually to formation of an abnormal communication with an adherent viscus. During an acute episode, a localized abscess may be formed which subsequently ruptures into a nearby viscus or even into a distant pelvic or thoracic viscus.

Gallstones impacted in the cystic duct may produce empyema of the gallbladder, causing gangrene of the cholecystic wall and perforation into an adjacent viscus. Behrend and Cullen[4] have pointed out that obliteration of the cystic duct probably plays an important part in the formation of a fistula between the gallbladder and the common bile duct by producing increased pressure of the contents of the gallbladder.

Choledochoduodenal fistula may result either from perforation of a duodenal ulcer into the common bile duct, or from erosion of the wall of the common bile duct by a stone and the subsequent perforation of the stone into the duodenum. Obstruction of the common bile duct is an important factor in maintaining a fistula: the fistula remains patent as long as the common bile duct remains obstructed.

Of the 18 patients having internal biliary fistula, 12 had chronic cholecystitis and cholelithiasis, three had duodenal ulcer, and three, respectively, had carcinoma of gallbladder, colon, and pancreas. Of the 12 patients having cholecystitis and cholelithiasis, five had only remnants of the gallbladder. In all 18 patients, dense adhesions to the adjacent organs were present. In six patients, stones and dilatation of the common bile duct were identified.

Signs and Symptoms

There are no characteristic clinical symptoms other than those that usually are associated with nonfistulous biliary disease. Of the 18 patients, 10 had had symptoms of biliary disease for 10 years or longer; the longest duration of symptoms was 34 years. The symptoms, in order of frequency, are presented in Table 2.

Table 2.—*Frequency of leading symptoms*

Symptoms	No. of patients
Pain—recurrent in right upper quadrant, radiating through to the back	17
Indigestion	17
Nausea or vomiting	12
Jaundice	7
Mass in right upper quadrant	4
Constipation	2
Diarrhea	2
Anemia	1

Acute intestinal obstruction resulting from gallstones, the passage of a stone via the rectum, or the passage of gallstones into an abscess cavity in vomitus, or through a sinus, is evidence of the formation of a biliary fistula. An internal biliary fistula may produce cholangitis, hepatitis, intestinal obstruction, hemorrhage due to erosion of a nearby vessel, and localized peritonitis. In cases of cholecystocholedochal fistula, a stricture or complete obliteration of the common bile duct may occur, resulting in jaundice and other signs of obstruction. Despite the variety of the above-mentioned complications, many patients are symptom-free for years, and occasionally the fistula will close spontaneously.

Table 3. *— Diagnostic accuracy of preoperative roentgen findings*

Findings		No. of cases
Correct		15
Presence of barium in biliary tract	10	
Presence of air in biliary tract	5	
Incorrect		3
Absence of air or barium in biliary tract	3	
TOTAL		18

Fig. 1. Plain film. Gas in distended hepatic radicles **demonstrates abnormal** communication between duodenum and biliary tree, shown by arrow **at a.**

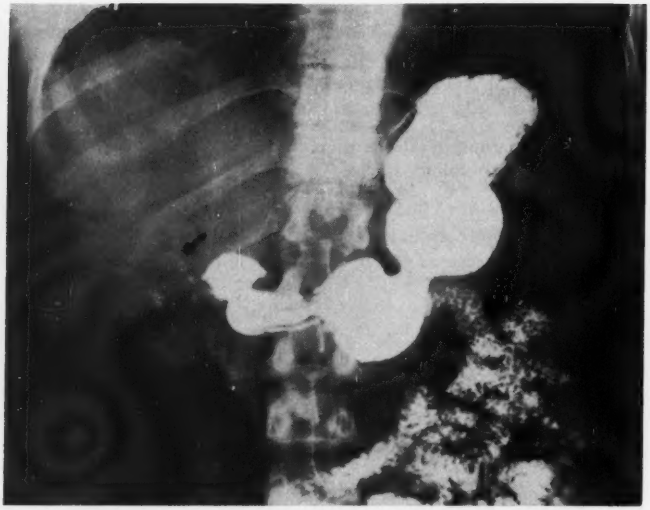

Fig. 2. Upper gastrointestinal tract, showing deformity of duodenal bulb with a fistulous communication between the duodenum and the biliary tree.

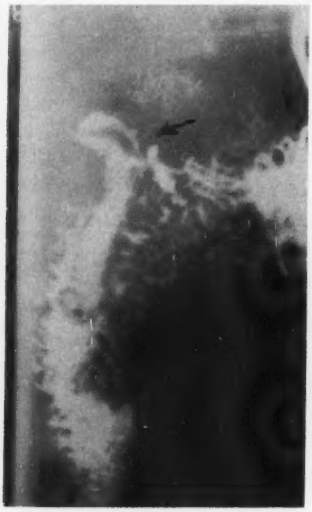

Fig. 3. Spot film taken at time of gastrointestinal examination. Note that barium has entered the common bile duct via a fistula from the duodenum, and fills the common duct to the ampulla of Vater.

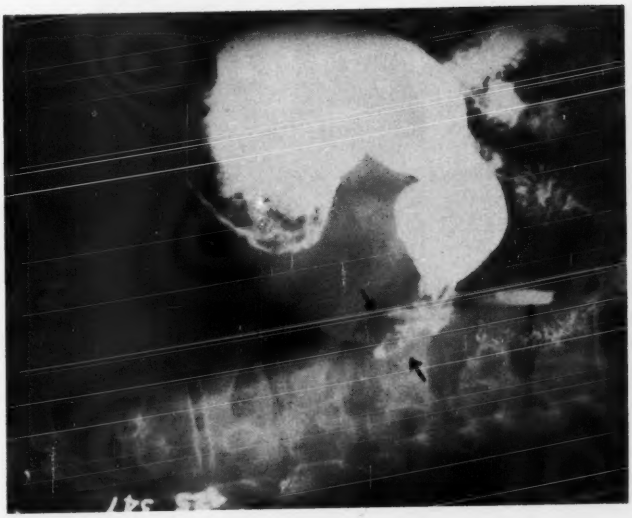

Fig. 4. Right anterior oblique film, showing barium in the common bile duct; it has entered via a duodenal fistula.

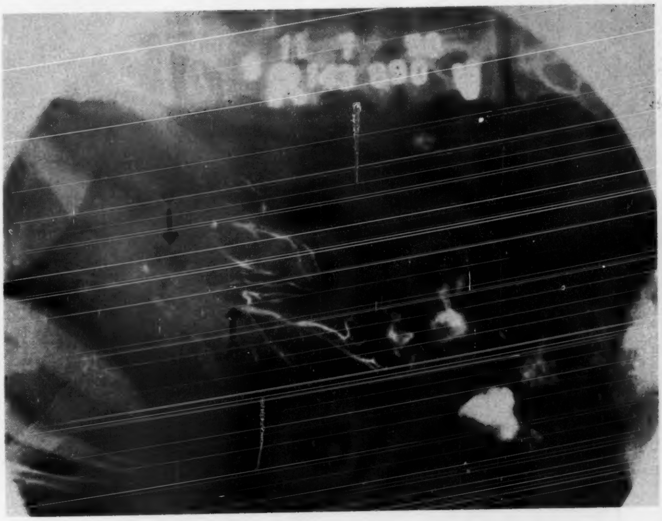

Fig. 5. Cholecystogram of upper gastrointestinal tract showing no evidence of cholecystic function. Air is visible in the hepatic radicles at **a** and barium at **b**.

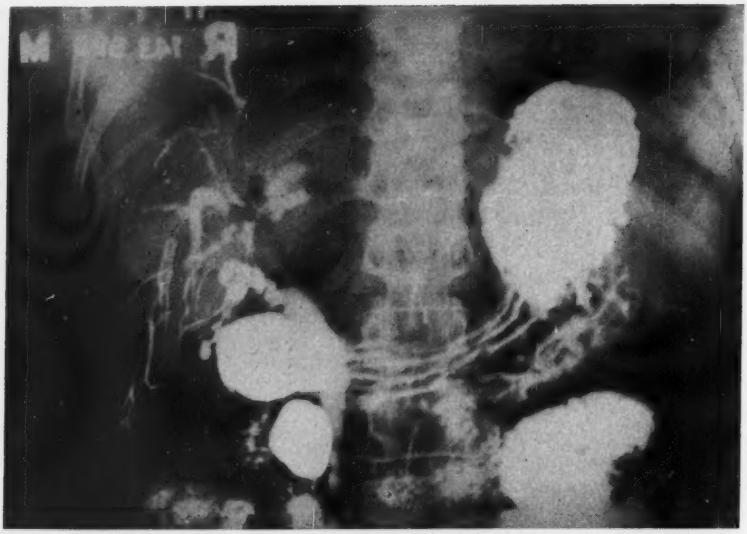

Fig. 6. Barium is in the biliary tree; it has entered via a fistula from a duodenal ulcer, and barium is in the diverticulum of the third portion of the duodenum.

Fig. 7. Right anterior oblique film showing deformity of the duodenal bulb with fistulous communication between the duodenum and the common bile duct.

Diagnosis

Before the development of roentgenography, the diagnosis of internal biliary fistula usually was made only during surgery or at postmortem examination. Today, if the communication is with the gastrointestinal tract, roentgenograms in most instances will reveal the abnormal fistulous communication, following the administration of barium orally or by rectum. Scout films of the abdomen may reveal air in the region of the gallbladder or of the hepatic radicles—a diagnostic sign that indicates regurgitation of the intestinal contents into the biliary tract. Michels and Hoerr[1] mentioned the diagnostic value of the presence of air in the biliary tree and especially in the interlobar ducts, and also noted that occasionally bacillary infection of the cholecystic wall will produce gas that outlines the billiary tree.

The correct diagnosis was made by roentgen examination in 15 of our 18 cases (Table 3). Figures 1 through 7 are examples of the diagnostic value of the roentgenograms.

Operative cholangiography has proved useful; it not only serves to confirm the diagnosis but also to detect the presence of remaining calculi or other abnormalities of the biliary tract.

Treatment

When the fistula produces complications that cause clinical symptoms and signs, ordinarily the treatment is surgical. Cholecystectomy and closure of the abnormal duodenal or colic opening is the preferred procedure for the cholecystoduodenal and cholecystocolic fistulas. Subtotal gastrectomy with vagotomy and gastrojejunostomy is the preferred procedure for the choledochoduodenal type of duodenal ulcer, because the biliary tract will be protected from the reflux of gastrointestinal contents. The exclusion-type subtotal gastrectomy and vagotomy promote the healing of the offending duodenal ulcer. When stones are present in the common bile duct, operative cholangiography, removal of stones, and T-tube drainage, are indicated.

In 14 of our cases the treatment was surgical (Table 4). The four other patients refused surgery.

Table 4. *— Types of surgical treatment in 14 cases*

Procedure	No. of cases	Recovery, no. of cases	Death, no. of cases
Cholecystectomy, excision of fistula and closure of duodenal or colic opening	11	9	2
Exclusion-type subtotal gastrectomy	1	1	—
Ileotransverse colostomy	1	1	—
Biopsy and drainage of pancreas	1	—	1
TOTAL	14	11	3

Results

Of the four patients who did not undergo surgery, two were lost to follow-up; one died one year after the examination, from carcinoma of the gallbladder and metastasis to the liver; and one was asymptomatic five years after the initial examination.

Of the 14 patients who underwent surgery, 11 have done well for one month to six years since operation. Three died: one from hepatorenal failure on the second postoperative day; one from carcinoma of the pancreas on the sixty-seventh postoperative day; and the third from an undetermined cause (autopsy was not performed) on the fourth postoperative day.

Summary

Eighteen cases of internal biliary fistula are reported and discussed in relation to etiology, diagnosis, and treatment. Although the disease presents no characteristic clinical picture, the roentgen findings offer a reliable means of diagnosis. When the fistula produces complications that cause clinical symptoms and signs, and the patient's general condition permits, surgical treatment is indicated.

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UNILATERAL EXOPHTHALMOS AS THE PRESENTING SIGN IN LEUKEMIA

Report of Two Cases

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UNILATERAL EXOPHTHALMOS rarely occurs as the initial sign of leukemia, although exophthalmos occasionally develops during the course of leukemia—Reese[1] reports the occurrence in 2 per cent of patients having lymphocytic leukemia. Since it is usually the ophthalmologist who is called upon to determine the cause of exophthalmos, the fact that it may be the presenting sign in unsuspected leukemia is of particular importance to him. The present report describes two unusual cases in which unilateral exophthalmos was the first sign of leukemia. These occurred in two seven-year-old children, a boy and a girl. The exophthalmos was persistent in the boy and intermittent in the girl.

Report of Cases

Case 1. A seven-year-old boy was first examined in the Department of Ophthalmology on November 6, 1952. His parents stated that he had had some protrusion of the right eye for about two weeks, but that his general health had been excellent (Fig. 1 a).

Table 1 gives the results of the ocular examination. No mass was palpable, and bruit was questionable. Examinations of the extraocular muscles and the ocular fundi revealed no abnormalities.

The patient was examined in the Department of Neurological Surgery by Dr. W. James Gardner, and no evidence of intracranial pathology could be found. The examination by Dr. Harold E. Harris of the Department of Otolaryngology disclosed no evidence of mucocele or of other pathologic condition in the sinuses.

Laboratory studies revealed a red blood cell count of 3,700,000 and a white blood cell count of 6,150 per cu. mm.; a negative serology; a hemoglobin content of 9.6 gm. and a blood sugar level of 67 mg. per hundred milliliters. The findings on roentgen study of the chest, sinuses, skull, and optic foramina were normal.

On November 17, 1952, the patient was admitted to the hospital for possible exploration of the orbit. Although the ocular measurements were unchanged at that time, the right eye appeared to be somewhat more prominent than when first examined (Fig. 1 b). At the recommendation of Dr. Robert D. Mercer of the Department of Pediatrics, a bone marrow examination was made preoperatively. The results were suggestive of neuroblastoma or possibly, leukemia; and orbital exploration was not performed. A special blood cell count revealed 56 per cent lymphoblasts, and a diagnosis of acute leukemia was made.

A course of roentgen therapy to the orbits was completed on November 26, 1952 (Fig. 1 c). By December 9, 1952, the anteroposterior measurement of the right eye was 17 mm., a reduction of 4 mm.

(a) (b) (c)

Fig. 1. (Case 1) Photographs of patient taken (a) on November 11, 1952, (b) on November 19, 1952, and (c) on November 26, 1952.

Table 1.—*Results of initial ocular examination (Case 1)*

	Right eye	Left eye
Visual acuity	6/6	6/6
Fissures	13 mm.	8 mm.
Anteroposterior (Hertel exophthalmometer) measurements	21 mm.	15 mm.

During the next few months the patient was hospitalized a number of times to receive blood transfusions, 4-amino-pteroylglutamic acid, and nitrogen mustard; however, his course was progressively downhill and he died on May 24, 1953, seven months after the initial examination.

Diagnoses from the postmortem examination were: (1) Subacute granulocytic leukemia, evidenced in bone marrow, spleen, liver, lymph nodes. (2) Bronchopneumonia, focal diffuse, leukemic type. (3) Petechial hemorrhages in the heart, pericardium, and stomach. (4) Lipoid depletion in adrenal. (5) Ulcerations of skin of left arm and leg.

Case 2. A seven-year-old girl was first examined here on April 2, 1954. Her parents stated that she had had intermittent slight protrusion of the left eye for about one month: the eye would protrude for a period of eight or nine hours after which it would again be normal. They believed that there was no appreciable protrusion on the day of examination. Her general health had been excellent.

Table 2 gives the results of ocular examination which demonstrated slight exophthalmos of the left eye. No mass was palpable, and no bruit was heard. The ocular fundi were normal.

Table 2.—*Results of initial ocular examination (Case 2)*

	Right eye	Left eye
Visual acuity	6/15	6/15
corrected to	6/9 with	6/9 with
	+ .25 sph ⊂ + 2.25 cyl, ax 95	+ 2.25 cyl, ax 85
Fissures	8 mm.	7 mm.
Anteroposterior (Hertel exophthalmometer) measurements	17 mm.	19 mm.

Examination by Doctor Mercer in the Department of Pediatrics revealed no further abnormalities. Special blood studies revealed a red blood cell count of 4,330,000 per cu. mm.; a hemoglobin content of 11.6 gm. per hundred milliliters; and a white blood cell count of 9,950 per cu. mm., in which were identified 5 per cent blast cells, 6 per cent atypical cells, 3 per cent early cells. A study of the bone marrow revealed a slight increase in blast cells, but an exact diagnosis was not possible. The serology was negative, and the blood sugar level was 91 mg. per hundred milliliters. Findings on urography and on roentgenography of the skull and long bones were normal.

One month later the child's condition was essentially the same, except that the exophthalmos of the left eye was more noticeable with a 3 to 4 mm. difference between the two eyes, and the white blood cell count was 4,600 per cu. mm., consisting of 6 per cent blast and early cells.

Within the next two months (Fig. 2 a) there was no change in the test results, except that roentgenograms revealed haziness of the left ethmoid and maxillary sinuses and a mass that was palpable under the left supraorbital ridge. Biopsy of the mass revealed leukemic infiltration. A course of nitrogen mustard therapy was started; the exophthalmos receded for three months.

On November 4, 1954, 25 per cent blast cells were found in the peripheral blood, and a diagnosis of granulocytic leukemia, subacute type, was made from examination of the bone marrow. Roentgen therapy was then given to the left orbit and the exophthalmos again diminished (Fig. 2 b).

Within three months the white blood cell count had increased to 46,000 per cu. mm., with 72 per cent blast cells. The hemoglobin content was 3.5 gm. per hundred milliliters (Fig. 2 c). The course was progressively downhill and she was hospitalized several times to receive roentgen therapy to the left knee, left ankle, dorsal spine, and ears because of pain. Twice she developed subconjunctival hemorrhages in the right eye. She died on March 1, 1955, 11 months after the initial examination. The final diagnosis was granulocytic leukemia. No autopsy was performed.

(a) (b) (c)

Fig. 2. (Case 2) Photographs of patient taken (a) on June 30, 1954, (b) on November 12, 1954, and (c) on February 1, 1955.

Survey of the Literature

The coexistence of exophthalmos and leukemia is reported every year, both in this country and abroad. Forkner[2] in 1938 presented a comprehensive historical account of the published literature. Reese and Guy[3] in 1933 reported a 69-year-old man who had lymphocytic leukemia in whom unilateral exophthalmos was the presenting complaint. They also reported a 19-year-old man having granulocytic leukemia whose presenting complaint was a five-day history of visual loss in one eye; six days after initial examination the patient developed exophthalmos in the other eye. They stated that exophthalmos as a complication of granulocytic leukemia is exceedingly rare. Cohen[4] in 1934 reported the case of a patient with lymphocytic leukemia who had a leukemic growth between the globe and the orbit.

O'Brien and Leinfelder[5] in 1935 reviewed 82 consecutive cases of unilateral exophthalmos. Blood dyscrasias were present in 7 of 51 patients whose exophthalmos was noninflammatory. Apparently two of those with blood dyscrasia had the exophthalmos as the initial sign of the disease.

Kandel[6] reported three cases of chloroma along with a review of 175 cases in the literature. Chloroma may produce exophthalmos, since it is a variant of granulocytic leukemia characterized by a deposition of greenish-yellow tumor-like masses in the skeleton, especially in the skull and orbital regions, in the lymph nodes, and in the viscera.

Randolph[7] in 1938 analyzed reports of 71 consecutive patients having unilateral exophthalmos, none of whom had leukemia.

McGavic[8,9] reported 21 patients with lymphomatous diseases involving the orbit. One of two with leukemia had lesions in the eyelids three years before other parts of the body became involved.

Discussion

Unilateral exophthalmos always presents a difficult diagnostic problem because it is a manifestation common to all space-taking lesions of the orbit.[10]

The difficulty is compounded by the more than 75 possible etiologic factors that come into consideration.[11,12] Seldom if ever can a diagnosis be established after a brief examination, and more often than not the ophthalmologist must call upon the aid of colleagues from other specialties, such as endocrinology, hematology, neurosurgery, otolaryngology, pediatrics, and radiology, if certain etiologic possibilities are to be ruled in or out and the true diagnosis is to be obtained. One of the common causes of unilateral exophthalmos is Graves' disease. This, even without hyperthyroidism, may be differentiated from other causes by the use of the triiodothyronine suppression test described by Werner.[13] The failure of this drug to suppress the radioiodine uptake confirms the diagnosis of Graves' disease; however, the disease cannot be excluded if there is a significant decrease in the radioiodine uptake such as that which occurred in two of our patients with Graves' disease.

Our two cases reported here demonstrate the importance of hematological consultation in evaluating unilateral exophthalmos and the wisdom of performing complete and repeated blood studies, including examination of the bone marrow. In particular, an accurate differential white blood count may obviate the need for other tests and for what would be useless surgery.

Summary and Conclusions

Unilateral exophthalmos rarely is the presenting sign in leukemia, although exophthalmos occasionally develops during the course of the disease. Reports are presented of two children having leukemia in whom unilateral exophthalmos was the initial sign. In one child the exophthalmos was intermittent, and in the other it was constant. Patients whose presenting sign is exophthalmos should have complete blood studies including examinations of bone marrow, because the findings on these studies may prevent unnecessary orbital exploration.

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A MASKING TECHNIC FOR PHOTOGRAPHIC REPRODUCTION OF ROENTGENOGRAMS

Preliminary Report

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ROENTGENOGRAPHIC detail that ordinarily cannot be reproduced by conventional photographic methods may at times be preserved by means of a masking technic. The method described here is not entirely original, but is a modification of several previously described technics aimed at development of a simple yet effective process.

The basic problem with which radiologists and medical photographers are faced is the difference in contrast between roentgen film, which is viewed in transmitted light, and photographic paper, which is viewed in reflected light. The brightness range of a roentgenogram may run from 1 to 1000 or more; whereas, that of a photographic print may run from less than 1 to 50.[1] To offset this wide difference in contrast ranges, it has been common practice in making prints of roentgenograms to use a *dodging* or *blocking* procedure that decreases the exposure of the less dense areas of the roentgenogram. Dodging usually is accomplished by passing the hand or other opaque object between the source of light and the printing easel. Dodging is a type of masking procedure; in photographic terminology a *mask* is a device for screening light to secure visualization of details of contrast that otherwise would be lost in the process of reproduction. We currently are using a *positive film mask*. Exposure is made simultaneously through both a negative film and a positive film (mask) of the roentgenogram. This preserves details that otherwise would be beyond the range of contrast of the paper.

The technic of using a positive mask, according to Frantzell,[2] was in use in 1929: Laurell[3] used positive film masks but he did not publish his procedure. Other workers [4-9] used a similar procedure.

Laurell[3] apparently encountered difficulty in precisely matching the negative and the positive for printing; even a fraction of a millimeter of displacement produces an effect of depth. Theobald,[4,5] and Secord, Moss, and Diamond[6] utilized the effect of depth by deliberately shifting their films slightly off register. Even earlier, in the days of glass plates, a similar result was achieved by Holland.[9] By printing through positive and negative plates placed back to back,

with a light source inclined at an angle of about 45 degrees, he obtained striking relief effects. However, none of these investigators reported attempts to diffuse the image of the positive, which is an essential step of our technic.

Frantzell[2] tried to obscure the effect of depth by exposing the positive out of focus; Maurer, Yule, and Cornwell[1] used two separate masks: a sharp "highlight" mask, and a diffuse "area" mask. All of the previous authors have reported making contact (same-sized) reproductions only—a procedure that entails using films up to 14 by 17 inches—and their technics, therefore, are not suited to our large volume of work. We find that copies that are reduced in size are more conveniently processed and are less expensive.

Technic

A small-sized negative of the roentgenogram is made in the conventional manner.* It is a copy of the roentgenogram but with the densities reversed. The dry negative is placed emulsion side down on a contact printer and a sheet of unexposed film is placed emulsion side down over the negative (Fig. 1). The second film is exposed; it is processed in a normal developer and is dried. It is a *positive mask* film and its densities are homologous to those of the roentgenogram.

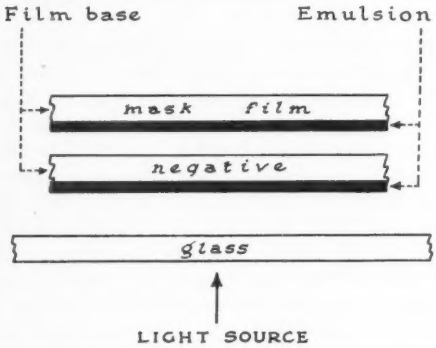

Fig. 1. Diagrammatic cross section of arrangement of negative and mask for contact printing.

The negative and the positive mask then are positioned in as exact alignment as possible (the emulsion side of each is down) and they are taped together. Reproduction is made by printing through the two films (Figs. 2 and 3).

Comment

We use a very light positive film as the mask. The density range of the positive should be approximately one third to one half that of the negative. A mask that has a range of density that is too high tends to overcorrect the final print and produces a flattening of tonal range; a mask of lower density values is

* *Kodak Commercial Ortho Film is satisfactory, but any film of similar characteristics may be used.*

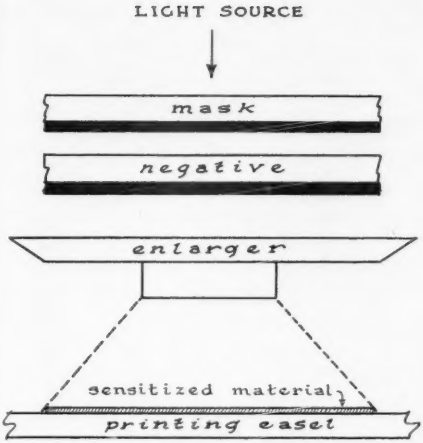

Fig. 2. Diagrammatic cross section of arrangement of negative and mask for printing with an enlarger.

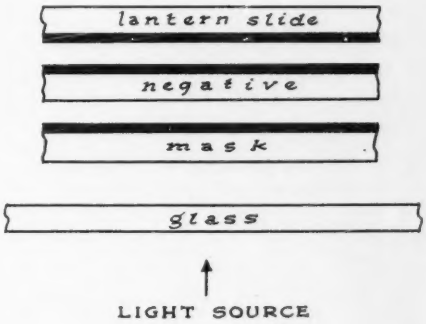

Fig. 3. Diagrammatic cross section of arrangement of negative and mask for contact printing of lantern slides.

preferable because undercorrection produces better results than does overcorrection.

In making the positive, the image is diffused to the proper degree during the passage of light through the film base of the negative. The diffusion in the positive does not interfere with the sharpness of the final reproduction; it facilitates proper registering of the mask with the negative, and detail from the negative appears sharper in the reproduction than in one made by conventional printing[8] (Figs. 4-9). The improvement is based on the fairly uniform deposit of silver that covers the edges of the fine details in the mask. Thus, when printing through the mask, the dense areas of the *negative* can be given the proper exposure without overexposing the finer details. The prints made by this method are, in respect to sharpness and clarity, rather comparable to those obtained by xeroradiography.[10] (Xeroradiography is a method of producing

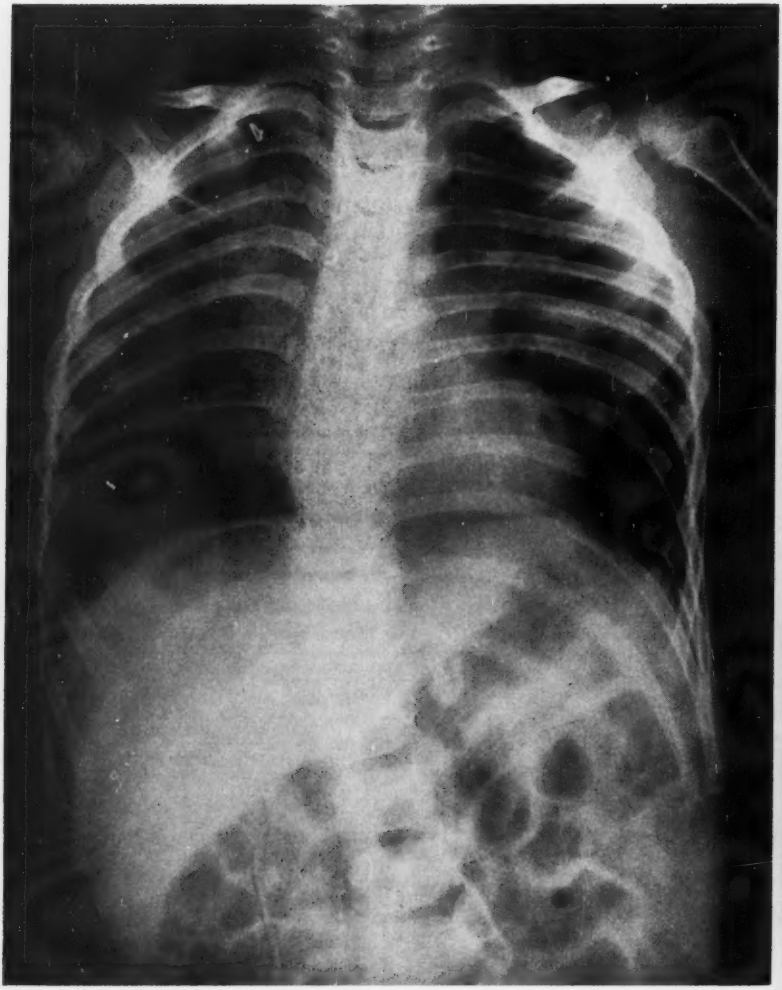

Fig. 4. *Conventional print*

Fig. 4. Two reproductions of one roentgenogram of patient having bronchopneumonia. The masked print has clearer visualization of the pathologic condition, more detail of the bony thorax, and strikingly more detail of the soft-tissue shadows of the shoulders.

Fig. 4. *Masked print*

roentgen images without using processing solutions. Xeroradiographic prints are made by transfer of the powdered image from the metal plate.) Our prints also possess many of the features that are provided, at considerably greater cost, in roentgenographic copies made by an electronic process that controls the exposure for each minute region within the printing area.[11]

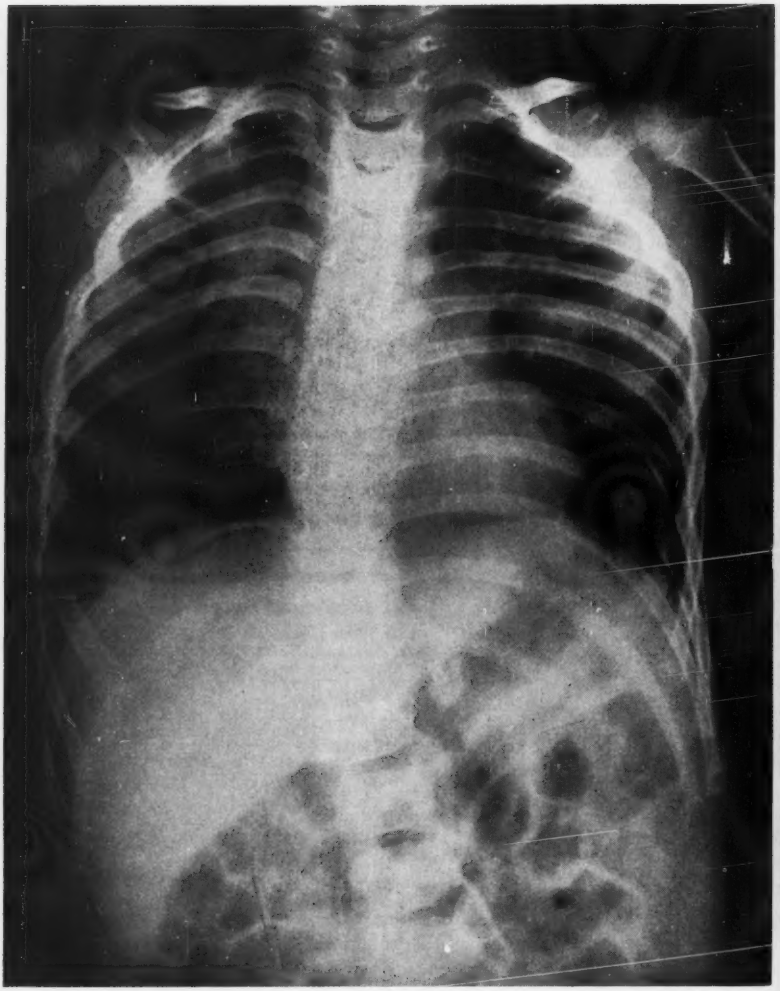

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Fig. 5. Two reproductions of one roentgenogram of a knee. The masked print shows more detail than does the conventional print, not only in the bones but also in the soft tissues.

Fig. 5. *Conventional print*

Fig. 6. *Conventional print*

Fig. 6. Two reproductions of one roentgenogram of a pelvis. The conventional print shows extreme range of contrast densities that are softened in the masked print.

Fig. 5. *Masked print*

Fig. 6. *Masked print*

Fig. 7. *Conventional print*

Fig. 7. Two reproductions of one ventriculogram. Both prints have about the same visualization of the air outline of the ventricles, but the masked print shows more clearly the diploic spaces of the skull and more detail in the first cervical vertebra.

Roentgenograms having a great range of contrast are the most suitable for making prints by our method. The technic is even more effective in making transparencies or lantern slides, in which details are seen by transmitted light.

Summary

A simple, inexpensive, positive masking technic is described which improves the quality of photographic reproduction of roentgenograms.

Fig. 7. *Masked print*

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Fig. 8. *Conventional print*

Fig. 8. Two reproductions of one femoral arteriogram showing considerable arteriosclerotic disease in the superficial femoral artery. Detail of the portion of the artery overlapping the bones is better on the masked print than on the conventional print.

Fig. 8. *Masked print*

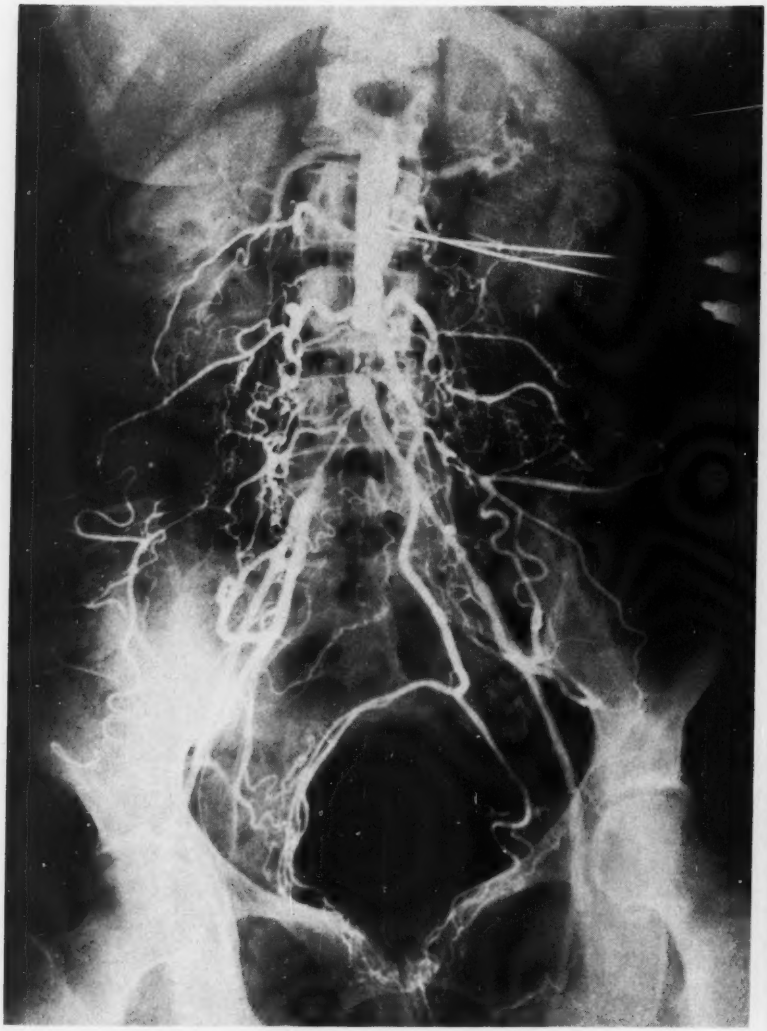

Fig. 9. *Conventional print*

Fig. 9. Two reproductions of one roentgenogram of a patient having thrombosis of the aorta. The multiplicity of collateral channels is more evident on the masked print than on the conventional print.

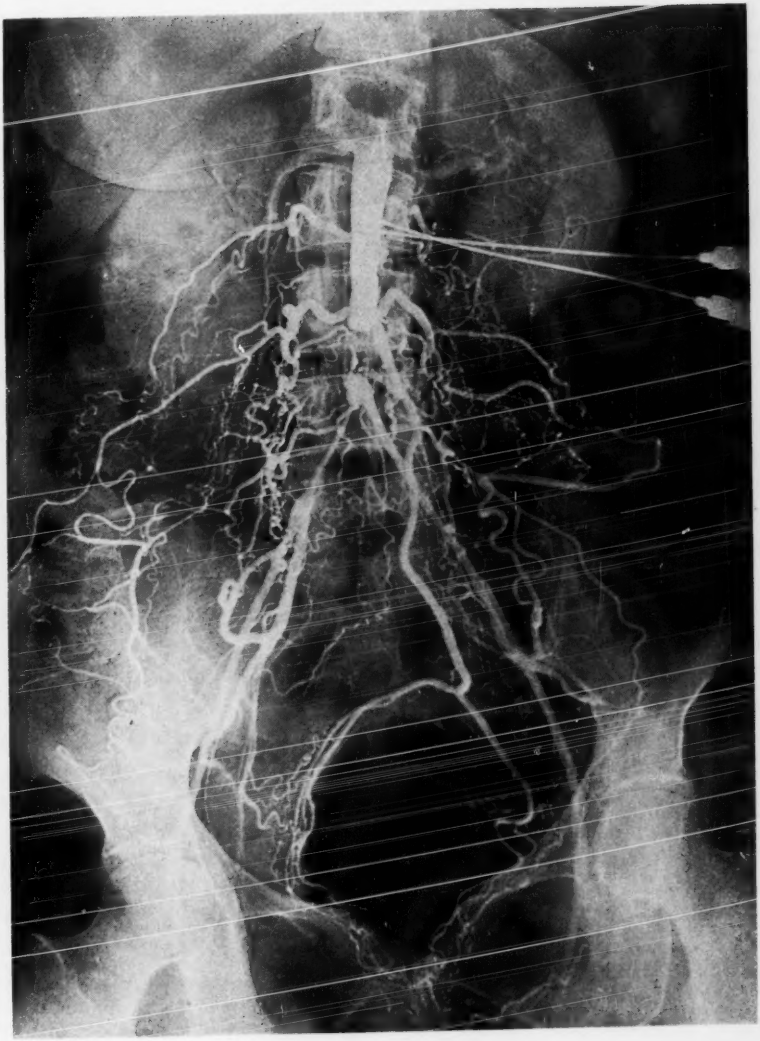

Fig. 9. *Masked print*

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PROGRAM AND PROCEEDINGS OF THE SCIENTIFIC SESSIONS OF THE FIFTH ANNUAL FELLOWSHIP REUNION OF THE FRANK E. BUNTS EDUCATIONAL INSTITUTE

September 9 and 10, 1955

Friday, September 9

— ABSTRACTS —

Morning Session

F. A. LeFevre, M.D., *Presiding*

1. INTRA-OSSEOUS VENOGRAPHY. Robert Schobinger von Schowingen, M.D., Buffalo, New York.

Intra-osseous venography is a new and simple technic that renders visible venous pathways that have partially or completely escaped visualization by other means. The technic of intra-osseous venography is as follows: After sedation of the patient with Demerol hydrochloride and Seconal sodium, a bone marrow aspiration needle is introduced, under local anesthesia, into the medullary cavity of the selected bone. Correct positioning of the needle is verified by aspiration of bone marrow; then 10 to 15 cc. of 50 to 70 per cent Urokon sodium is injected under constant moderate pressure. During injection of the last 3 or 4 cc., the roentgenograms are taken. No untoward effects were noted, and none should be expected if the necessary precautions against idiosyncrasies to the contrast medium or local anesthetic agent are observed.

Intra-osseous venography was performed in order to study: the changes affecting the azygos veins in the presence of mediastinal or pulmonary tumors; the vertebral plexi in normal and in pathologic conditions; the possibility of demonstrating isolated bony metastases much earlier than is possible by conventional methods; and the possibility of localizing pelvic tumors more adequately.

The area of visualization by intra-osseous venography is determined by the site of injection of the contrast medium (Fig.), as follows:

Intra-osseous venogram. Introduction of contrast medium into lower dorsal spinous process of normal patient. External vertebral plexus is moderately well demonstrated while the internal vertebral plexus is extremely well visualized over at least three vertebral spaces. From this latter plexus, the medium is drained into the azygos vein through several intercostal veins.

Site of injection and positioning of patient	Area of visualization
Ninth or tenth rib in the right midaxillary line, with the patient in supine position (medium passes through corresponding intercostal veins)	Azygos vein
Injection similar to the above, but in the left midaxillary line	Hemiazygos vein
Spinous process of D-11 or D-12, with the patient in a straight lateral position (right side down if pathologic condition is on right side, or vice versa)	Azygos system

Any dorsal or lumbar spinous processes	External and internal vertebral plexi in area corresponding to site of injection
Protuberances of peripheral bones	Superficial and deep venous circulation of that extremity
Iliac crest, greater trochanter or pubic bone (simultaneous bilateral injections provide best results)	Pelvic venous system

The following conclusions are based on the review of some 150 injections. (1) In patients having certain types of mediastinal and pulmonary tumors, obstruction of the azygos vein can be demonstrated. (2) Malignancies involving the spinal cord and possibly the vertebral bodies may produce an obstruction to the flow of contrast medium within the internal vertebral plexus at the level of the lesion. The medium is deviated distally, with resultant filling of the inferior vena cava, ascending lumbar veins, or azygos vein at a lower level. (3) Localized malignant processes of bone may cause an obstruction of the regional veins, interruption of the intramedullary diffusion of contrast medium, and the development of collateral circulation.

The great potentialities, the simplicity of technic, and the relative safety of intraosseous venography certainly invite further investigative work.

* * *

2. AN UNUSUAL CASE OF PERIARTERITIS NODOSA. Salvatore R. La Tona, M.D., Niagara Falls, New York.

The multiplicity of the signs and symptoms of periarteritis nodosa is a constant challenge to the diagnostic acumen of the physician. The case to be reported illustrates this challenge and is unusual in that the patient had nearly all of the protean manifestations of periarteritis nodosa and that, in spite of severe recurrences, he survives five years after the onset.

Periarteritis nodosa is described as a systemic disease affecting medium-sized and small arteries. Some (Zeek, P. M.: Am. J. Path. **22:** 777, 1952) consider it to be a syndrome of multiple etiologies and go so far as to delineate distinct etiologic subgroups. Although I, among others, agree with this concept, in practice overlapping symptomatologies make it difficult to distinguish these subgroups—as in the case to be described.

The patient is now 47 years old. Hemoptysis in June 1951 led to segmental lobectomy with removal of a lung cyst. However, a month later he developed muscle and joint pains with swelling of one joint, and subsequently purpura over both legs. Diagnoses of rheumatoid arthritis and thrombocytopenic purpura were suggested. These symptoms together with hemoptysis and hematuria were present in February of 1952, at which time the provisional diagnosis of periarteritis nodosa was established by biopsy. Since then, he has had recurrence of pains and purpura, left orchitis superimposed on testicular

hemorrhage, pneumonitis, transitory hypertension, peripheral neuritis with foot drop and laryngeal palsy, cerebral thrombosis with hemiplegia, and semicoma of undetermined origin. He continues to have foot drop, hoarseness, stiffness of the legs and recurrences of purpura and pain. His condition is deteriorating and he is becoming increasingly irritable.

At various times he had been mildly or severely anemic with normal or increased white blood cell counts and constant elevation of sedimentation rate. Platelet counts always have been normal. The urine has shown red blood cells and albumin on occasion. Chest roentgenograms have shown recurring cystlike areas, and electrocardiograms have shown slight myocardial changes. Biopsy of the gastrocnemius muscle showed typical vascular lesions with necrosis and leukocytic and eosinophilic infiltration and fibrin thrombi in skin and in muscle. No etiologic agent has been identified. However, he was given a sulfa drug at the time of operation in 1951.

Treatment has been supportive, with physiotherapy and courses of ACTH and cortisone, antacids and potassium chloride. At present he can still walk with a cane and a brace on the right foot.

* * *

3. SEIZURE STATES AND PREGNANCY. Cary Suter, M.D., Charlottesville, Virginia.

This study of the relationship of seizure states (convulsions) to pregnancy was suggested from a consideration of three general clinical observations: (1) Seizure states are predisposed by any condition that leads to retention by the body of an excess of sodium and water. During pregnancy and the premenstrual periods fluid retention often occurs, and in eclampsia abnormal retention of sodium and water reaches a peak. (2) The initial onset of the seizure states came during pregnancy, according to a number of patients. (3) Improved therapy for seizure states has made it possible for more women who are subject to this condition to marry and to undergo pregnancy with success.

Of a group of 1000 patients having seizure states who were seen under the Seizure Control Program in the State of Virginia, 107 had histories of pregnancy. The correlation between seizure states and the pregnancies is reported in the Table. Of the 20 patients in whom the seizures were definitely more severe during pregnancy, 14 had had seizures of the grand mal and 6 of the psychomotor types. Eight of the 17 patients whose seizure states had had their initial onsets during pregnancy and continued postpartum, had shown some clinical evidence of toxemia; 9 of these 17 patients had had grand mal seizures and 8 had had mainly psychomotor seizures. Of the eight patients with onset definitely related to eclampsia, six showed typical psychomotor seizures with temporal lobe electroencephalogram focus. From the findings in these 17 patients, it is evident that the prevention of severe toxemia of pregnancy will result also in the prevention of many seizure states.

The following principles govern the treatment of the woman with seizure states who becomes pregnant: (1) *Weight control.* Total gain in weight during pregnancy should not exceed 18 pounds, and sudden gain in weight should be avoided. Weight gain above

this limit should be counteracted by a strict low-sodium diet and, if necessary, diuretics or ion-exchange resins should be administered. To insure strict adherence to the above regimen and best results, the patient should be hospitalized. (2) *Drug therapy.* The anticonvulsant drugs must be administered regularly. If the patient cannot take the drugs orally because of nausea and vomiting or during labor, she should receive injections of sodium phenobarbital as a substitute. The administration of the anticonvulsant drugs or of phenobarbital is especially important just before, during, and immediately after delivery.

With careful medical supervision, most women with seizure states can experience a relatively normal pregnancy and delivery, without harm to mother or child.

Table.—*Correlation of seizure states and pregnancy*

Status of seizure state during pregnancy	No. of women
Not known	35
No change	28
Increased severity	20
Original onset	17
Increased incidence	7
TOTAL	107

* * *

4. DOES THE AORTIC HOMOGRAFT DEVELOP ARTERIOSCLEROSIS? An Experimental Study*. Edwin R. Fisher, M.D., Pittsburgh, Pennsylvania.

Evidence has rapidly accumulated of the immediately beneficial effects of aortic transplants. Most of these transplants are used to restore luminal continuity at sites of arteriosclerotic aneurysm or thrombosis. Since arteriosclerosis may be a metabolic disease, it seemed pertinent to study the fate of fresh and of lyophilized aortic homografts in rabbits having a metabolic arteriosclerosis experimentally induced from a diet containing 2 per cent cholesterol. Previous experimental studies of the fate of aortic homografts have not been concerned with the effects of experimental arteriosclerosis, and there has not been as yet full clinical evaluation of the development of arteriosclerosis in aortic homografts in patients.

The data show that aortic homografts in cholesterol-fed rabbits are more vulnerable to atherosclerosis than the remainder of the host's aorta or of the aortas of cholesterol-fed control animals. The lesions observed within the grafts were histochemically and morphologically identical with those that developed in control sites and in control animals. Further, it was conspicuously evident that fresh homografts were more severely affected

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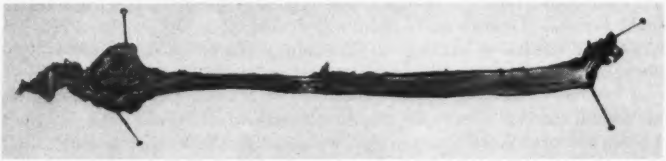
than were those prepared by lyophilization. Some of the fresh homografts developed aneurysmal dilatation (Fig.) and, in several, luminal occlusion resulted from the presence of large atheromatous plaques.



Aorta from rabbit (2 per cent cholesterol in diet for 70 days) with fresh homograft revealing aneurysm containing arteriosclerotic plaque. Small plaques are noted in remainder of host's aorta.

It is uncertain whether experimental cholesterol arteriosclerosis in rabbits can be identified with clinical arteriosclerosis in patients, so that it is not certain that human aortic homografts will show susceptibility to arteriosclerosis which has been demonstrated in the rabbit. However, as human aortic homografts of long duration become available, the clinical significance of this study can be finally evaluated.

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5. AN IMPROVED METHOD OF ADRENAL DENERVATION FOR ESSENTIAL HYPERTENSION*. Sherman A. Eger, M.D., The Jefferson Medical College, Philadelphia, Pennsylvania.

The purpose of this paper is to introduce an improved method of adrenal denervation and to describe its effects in patients having essential hypertension who were followed one to four years postoperatively. The method consists of surrounding each completely denervated adrenal with Oxycel cotton (oxidized cellulose) which, although absorbable, produces a cocoon-like barrier of fibrous tissue that is impenetrable to regenerating nerves and does not compromise the blood vessels. This method of denervation produces permanent changes in the adrenal—and thereby adds one important step to the method of denervation employed by the late Dr. George W. Crile whom some of us had the pleasure of knowing and the privilege of assisting in those operations about 25 years ago.

The operation is performed retroperitoneally through a five-inch incision parallel to and one inch below the twelfth rib. The lower edge of the adrenal appears when the kidney is rotated medially. All nerves are severed close to the adrenal under direct vision; those near to the central vein are severed last when all sides can be seen. The completely denervated adrenal is then encased in a one-inch-thick layer of Oxycel cotton (Fig.). A drain is inserted and the kidney is returned to its normal position. Operating time is about one hour. Patients are permitted out of bed on the second postoperative day, and are discharged from the hospital on the tenth postoperative day. An interval of four to six weeks is allowed before denervating the other adrenal, so that the first adrenal has had

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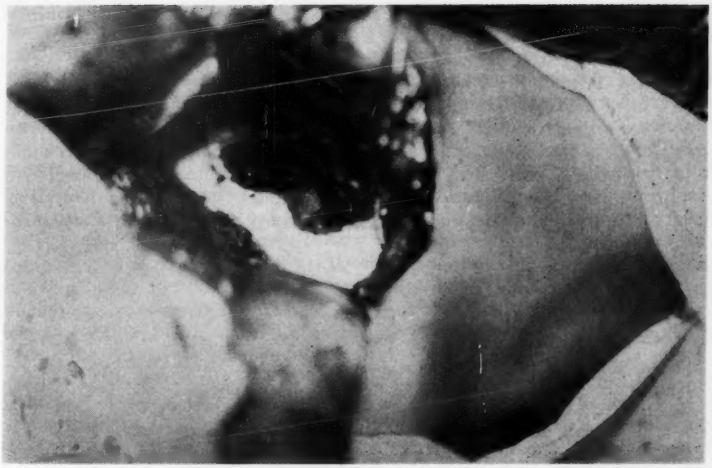

The completely denervated left adrenal has been covered with Oxycel cotton except for its anterior surface that is covered last. Upper pole of kidney with attached fat also is shown.

time to recover from any operative trauma. Adrenal replacement therapy was indicated in only one case. There was one operative death resulting from congestive heart failure that had existed preoperatively.

Adrenal biopsies at the time of denervation routinely showed cells of the cortex to be swollen and their characteristic arrangement to be indistinct; likewise, the medulla contained numerous large cells and nerves. Two years later autopsy in one case showed those same adrenals to have cells of normal size, in normal arrangement, and to be devoid of nerves.

The best postoperative results were obtained in hypertensive patients whose blood pressures preoperatively fell to unquestionably normal levels during the profound sleep produced by the Sodium Amytal test. Therefore, it is the degree of neurogenic element present that is important regardless of the age of the patient or of the duration of the hypertension. The degree to which the blood pressure falls during profound sleep indicates the effect that denervation of the adrenals will have on the hypertension. All five of the hypertensive patients (one half of the total series) whose blood pressures became normal during this test obtained a similar but seemingly permanent response after operation. The operation is contraindicated when the amount of fall in blood pressure during the sleep test is not of sufficient degree to influence favorably the present state and future course of the hypertension. Operating for advanced hypertension after serious organic complications have developed does about as much good as operating for cancer after it has metastasized.

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6. SURGICAL MANAGEMENT OF HYPERTENSION. J. W. Shirer, M.D., Pittsburgh, Pennsylvania.

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7. NEEDLE BIOPSY OF THE LIVER. John J. Grady, M.D., Lakewood, Ohio.

Needle biopsy of the liver should be performed in patients having or suspected of having the following conditions: (1) hepatic disease in which the findings on hepatic function tests are inconclusive; (2) hepatic disease in which the etiology is obscure; (3) jaundice; (4) cirrhosis (biopsy performed to estimate the prognosis and occasionally to evaluate therapy); (5) systemic diseases that are known to involve the liver, in which the usual procedures have failed to establish the diagnosis. One of the prime values of needle biopsy of the liver is the demonstration of malignancy, either primary or metastatic.

On the basis of findings on needle biopsy of the liver, the diagnoses in 151 patients were as follows:

Diagnosis	No. of patients
Cirrhosis of the liver	51
Degenerative diseases	31
Metastatic carcinoma	23
Normal hepatic tissue	21
Chronic inflammatory diseases	18
Extrahepatic biliary obstruction	2
Miscellaneous	5
TOTAL	151

No fatalities and only two serious complications were attributable to the procedure. In patients with a palpable liver and no tendency to bleed, the anterior subcostal approach with the Vim-Silverman needle is recommended.

Needle biopsy of the liver need not be confined to use in teaching or to research institutions, but can and should be part of the clinical investigation of patients with hepatic disease in any private hospital.

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8. THE THERAPEUTIC TRIAL FOR SUSPECTED AMEBIC DISEASE. Ferdinand J. Hruby, M.D., Cleveland, Ohio.

Within the past two decades amebic disease has been recognized as a problem that no longer has geographic limitations. The manifestations of this disease may be protean and the diagnosis difficult. Because of technical difficulties, attempts to isolate the amebic organism may be unsuccessful.

A presumptive clinical diagnosis of amebic disease and a therapeutic trial of anti-

amebic medication is justifiable in certain selected cases. A painstaking history with particular emphasis on foreign travel is essential. Amebic disease may produce symptoms mimicking functional gastrointestinal disease, and a diagnosis of psychoneurosis can mistakenly be made. Episodes of discomfort may occur weeks or months apart and are only partially relieved by antispasmodics, diet, and sedation. In addition, amebiasis may produce more conspicuous symptoms such as obscure fever, vague abdominal pain, diarrhea, and the signs and symptoms of hepatitis. Amebiasis, particularly amebic granulomas, may simulate certain surgical conditions. Ill-advised surgery has a high mortality rate in the presence of amebic infection.

The first patient had a diagnosis of psychoneurosis after she had been under observation in several institutions. She was a chronic complainer who had had episodal bouts of fatigue and vague intestinal symptoms. Twelve years previously, she had travelled extensively in South America. After fruitless clinical study, including warm stage stool examinations, she was placed on antiamebic treatment. Her response to this treatment was prompt and dramatic, and she has remained well for the past year since treatment.

The second case demonstrates how amebic disease may produce dramatic and severe symptoms. A 42-year-old dentist had suffered fever, aching, loss of weight, and marked asthenia for several weeks. All diagnostic studies were unrevealing and abdominal Hodgkin's disease was considered. On further inquiry, he stated he had been in the Navy and had served in the Philippines, but had had only rare episodes of mild diarrhea. He was placed on amebicidal treatment and the response was favorable following one course of antiamebic therapy. He has remained well for the past five years. In his case, the psychological trauma of a hopeless prognosis (Hodgkin's disease) and the possibility of a laparotomy were avoided.

The course of treatment in both of these cases consisted of five daily injections of emetine hydrochloride (1 grain) followed by carbarsone, 3¾ grains, twice daily for ten days. Recently, the use of emetine has been supplanted by other drugs including antibiotics and newer arsenical preparations (Fumagillin, Arsthinol, Carbomycin, etc.).

These two patients illustrate the fact that amebiasis may cause vague symptoms, that the disease may be difficult to diagnose, and that a course of antiamebic therapy can result in dramatic improvement. Despite negative laboratory findings, a therapeutic trial of antiamebic therapy is indicated in selected cases.

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9. CHRONIC GRANULOMATOUS LESIONS OF THE RIGHT COLON SIMULATING MALIGNANCY. J. A. Lehman, M.D., Philadelphia, Pennsylvania.

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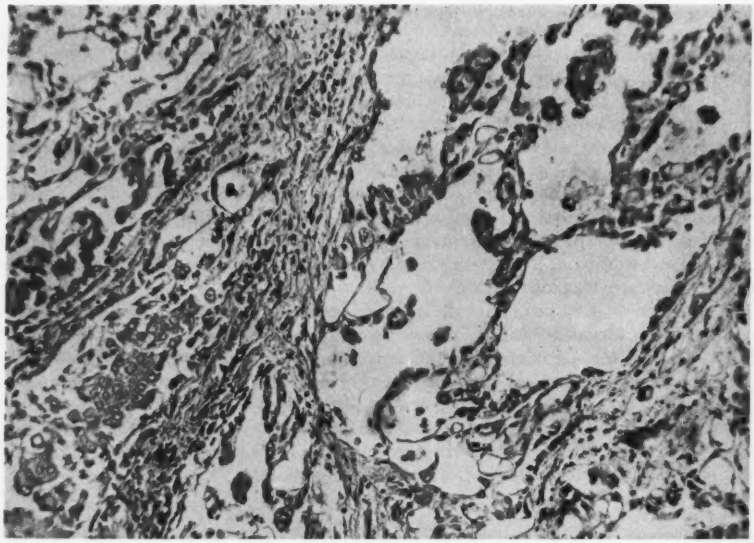
10. MESOTHELIOMA OF THE PERITONEUM. George W. Knabe, M.D., Dayton, Ohio.

Primary tumors of the mesothelium of the peritoneum are rare. They occur either as solitary growths or as disseminated nodules and plaques that characteristically involve the peritoneum superficially. Microscopically, these tumors often are similar to the proliferation of mesothelium in peritoneal inflammation, a similarity that aids in their identification. Sometimes they are so well differentiated that in biopsied material they

are mistaken for inflammatory processes. Localized and diffuse forms both of benign and of malignant types occur. The diffuse malignant growths always are fatal; they may have multiple sites of origin but it is more likely that they arise from peritoneal dissemination. Metastases usually are via lymphatics, although they rarely are more distant than to regional lymph nodes. The diffuse tumors often are accompanied by abundant mucoid ascitic fluid that contains hyaluronic acid.

The multipotentiality of the mesothelial cell accounts for great variations in microscopic appearance of primary peritoneal tumors. They can, however, be roughly grouped into five variants on the basis of histopathologic patterns: (1) *Tubular mesotheliomas*, (2) *Papillary mesotheliomas*, (3) *Fibrous mesotheliomas*, (4) *Undifferentiated mesotheliomas*, (5) *Mixed-type mesotheliomas* (Fig.).



Mixed-type mesothelioma, showing mesothelial-lined spaces together with nests of undifferentiated cells. Hematoxylin and eosin (X150).

Clinically, the benign peritoneal mesotheliomas produce only the signs and symptoms of an enlarging mass. Malignant forms occur in aged persons and usually cause vague gastrointestinal distress, abdominal swelling, and loss in weight; death occurs several months to a year after the onset of symptoms. The course resembles that of abdominal carcinomatosis. The diagnosis usually is made at autopsy, although the findings on biopsy at laparotomy or on cytologic examination of ascitic fluid may suggest the diagnosis. When the fluid is viscous, an attempt should be made to discover whether hyaluronic acid is present. In tissue specimens the character of the mucoid material should be studied by staining for mucin. The secretion produced by mesothelioma is of connective-tissue origin and does not react as does the epithelial mucin elaborated by adenocarcinoma. Localized mesotheliomas are adequately treated by wide excision, but in diffuse malignant forms the only treatment thus far shown to be of value is the intraperitoneal administration of radioactive colloidal gold.

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11. **COMMON CAUSES OF PAINFUL SHOULDER.** R. H. Jacques, M.D., Columbus, Ohio.

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12. **CHANGES IN THE ASPECT OF NEUROSURGERY OVER TWENTY-ONE YEARS.** W. B. Hamby, M.D., Buffalo, New York.

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Friday, September 9

— ABSTRACTS —

Afternoon Session

W. J. Engel, M.D., *Presiding*

1. A NEW METHOD FOR HEPATIC RESECTION*. John R. Robinson, M.D. and Harvey R. Butcher, Jr., M.D. (By Invitation), St. Louis, Missouri.

Control of hemorrhage is the greatest problem associated with resection of large segments of the liver. The hepatic suture technic of Terrier and Auvray (Terrier, F., and Auvray, M.: Rev. de chir. **18:** 706, 1898) with certain important modifications is similar to the one herein advocated. The method essentially involves a "cobbler type" of stitch inserted with a special, long, blunt, flexible wire needle (Fig.).

This technic has been used successfully in four cases and has the following advantages:

1. Hepatic vessels and large bile ducts are not punctured; the special needle readily passes through thick portions of hepatic parenchyma.

2. There is minimal danger of tearing the liver upon tightening this suture, because the pull is more equally distributed around the encompassed parenchyma.

3. No portion of the liver adjacent to the proposed line of resection escapes enclosure with this suture that is simple and can be rapidly placed.

4. There is minimal danger of hemorrhage and air embolism because the suture cannot slip, as it is continuous with the surrounding segments; therefore, large traumatic lacerations of the liver as well as tumors can be handled rapidly with minimal loss of blood.

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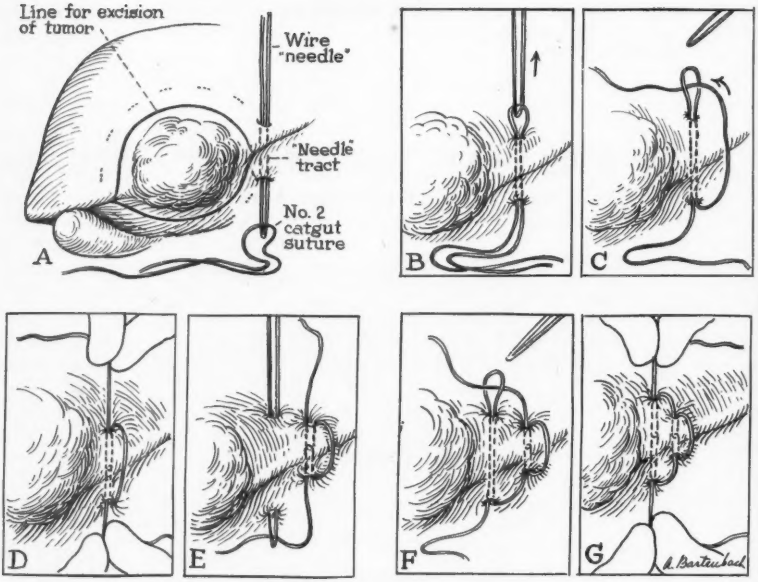


Technic

(A) A No. 16 silver wire, 20 inches long, is bent like a hairpin so that an open narrow loop is formed. This loop acts as the needle point, and is passed through hepatic parenchyma near (1 to 2 cm. proximal) to the line of hepatic resection. **(B)** The suture (No. 2 chromic catgut, full length) is passed through the "point" of the needle, and the needle is withdrawn back through the parenchyma so that a loop of catgut is pulled through the liver. **(C)** The free end of the suture is passed through the catgut loop previously drawn through the liver. **(D)** Both ends of the suture are drawn taut, allowing the interlocking junction to be drawn half way through the needle tract. **(E, F, G)** Tension is maintained on the previously placed suture while the above steps are repeated every 2 to 3 cm. until the portion of the liver to be resected has been completely encompassed. The liver is then transected 1 cm. parallel and adjacent to the suture line, and any small vessels that ooze on the cut surface are ligated.

* * *

2. THE NOBLE PLICATION OPERATION ON THE SMALL INTESTINE, FOR THE MANAGEMENT OF RECURRENT OBSTRUCTION FROM ADHESIONS. Robert P. Dutlinger, M.D., Harrisburg, Pennsylvania.

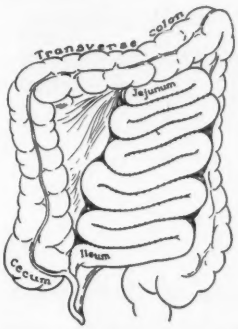
The management of recurrent obstruction from adhesions in the small intestine often presents a difficult and distressing problem. The majority of patients having these obstruc-

tions already have undergone a number of operations, and many have become psychoneurotic and addicted to drugs or to alcohol. However, if definite mechanical obstruction of the bowel is present, additional surgical treatment may be necessary.

The intraperitoneal instillation of substances such as mineral oil, papain, and amniotic fluid to prevent the formation of adhesions has not been successful. The usual procedure has been to divide the adhesions, thus freeing the kinked loops of bowel. Unfortunately, in many instances obstructing kinks have recurred, necessitating another similar operative procedure.

In 1937, Nobel (Noble, T. B., Jr.: Am. J. Surg. **35:** 41-44, Jan. 1937) described an operation that he termed *plication of the small intestine.* He reported having employed the procedure successfully in the management of adhesions. He stressed the principle that adhesions should be 'controlled' in the sense that they be localized to a previously determined area. His observations were not challenged or confirmed until five years ago when surgeons began to report encouraging results from the procedure.

The operative technic consists of mobilizing the small intestine, releasing all adhesions and plicating parallel loops throughout its length (Fig.). This operation may be of considerable magnitude. The technic may also be applied in a limited fashion, i.e., to a limited segment of small intestine rather than to its entire length. The latter method usually is employed at the time of an initial operation, such as for an abscess with adherent loops of bowel in the immediate vicinity. The detailed technic of intestinal plication has been discussed at some length in the literature. In general, it is considered preferable to employ a continuous suture of catgut placed midway between the mesenteric and antimesenteric borders of adjacent loops, assuring an ample loop at each end without kinking.



Schematic drawing showing
Noble method of plication of small intestine.

Twelve operations in which the Noble plication was employed have been performed at the Harrisburg Hospital, with postoperative follow-up from two to three years. Six of the procedures were segmental in type, while six were complete plications for recurrent obstructions. The results in the latter group are excellent in four, fair in one, and poor in one. The results of the six segmental type of plications cannot as yet be adequately evaluated; however, no obstructive symptoms have developed in any of the patients to date.

The Noble plication operation merits further investigation as a method of treating chronic or recurrent obstruction of the small intestine in carefully selected cases. The segmental type of plication seems to be a valuable adjunct as a primary procedure in the prevention of obstruction of the small bowel in patients with severely damaged visceral peritoneal surfaces.

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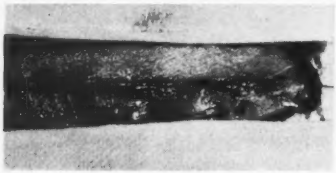
3. A NEW TYPE OF WOUND CLOSURE USEFUL IN PEDIATRIC SURGERY.

Houghton F. Elias, M.D., Beatrice, Nebraska.

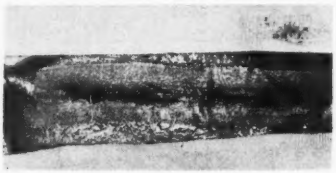
Recently a vinyl resin-base plastic material (Aeroplast) has been developed which is nontoxic (Choy, D. S. J., and Wendt, W. E.: U. S. Armed Forces M. J. **3**: 1241-1255, Sept. 1952.), nonsensitizing, and nonallergenic (Simon, S. W.; and Rinard, L. A.: J. Aviation Med. **24**: 530-531, Dec. 1953.). This film is insoluble in body fluids, and its solvent evaporates in seconds after it has been applied. It has proved useful as a sterile protective covering for burns and wounds.

It was thought that this plastic material might be an ideal dressing for pediatric surgery because it is waterproof, it will stand the stress of repeated flexing, it is easily applied, and it is simple to remove. The strength of the film has been measurably increased by the incorporation of gauze mesh in its construction. Wound edges that previously have been approximated by a subcuticular suture can be held in place with this reinforced film, so that the subcuticular suture can be removed immediately after application of the dressing (much in the same fashion that a tailor's basting stitch is removed) while maintaining accurate wound approximation.

This procedure is excellent for maintaining apposition of the edges in a reasonably short incision. The dressing is convenient, gives accurate approximation, maintains sterility over an aseptic wound and obviates subsequent removal of skin sutures from a struggling child.



A. 'Basting' stitch being removed.



B. Completed closure.

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4. ADVANTAGES OF PIRIDOCAINE HYDROCHLORIDE (LUCAINE) FOR SPINAL OR SADDLE BLOCK ANESTHESIA IN CERTAIN OPERATIONS.

W. R. T. Metzner, M.D., San Antonio, Texas.

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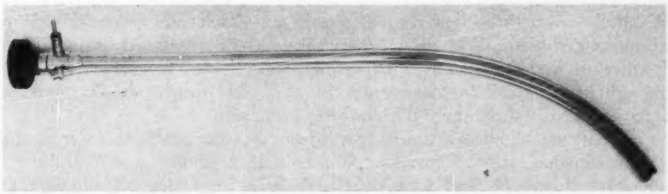
5. A NEW GASTROENTEROSCOPE.

Charles A. Lamb, M.D., Boston, Mass.

This report concerns a new gastroenteroscope that I have designed for use during abdominal surgery when it is necessary to determine the point of bleeding, to view the duodenum and its entering ducts, or to determine whether multiple lesions are present

in the colon. The new instrument has an unusually wide field of visualization and is not difficult to use. It is 54 cm. long, 1.5 cm. in diameter, and is curved in the distal third of its length, so as to permit easy visualization of portions of the gastrointestinal tract at some distance from its insertion (Fig.). A series of 12 prisms within the scope reflects the image accurately to the eyepiece.



Photograph of the gastroenteroscope.

The gastroenteroscope can be inserted into the stomach through a gastrotomy in the pyloric area, from which location the instrument can be passed into the esophagus and, by being reversed in direction, into the duodenum. To visualize the entire mucosal surface of the colon, two colotomies are necessary: one at the hepatic flexure, the other just below the splenic flexure.

For two days prior to gastroenteroscopy the patient should be given a nonresidue diet so that the gastrointestinal tract will be as free as possible from solid matter, and a nonabsorbable sulfonamide should be administered. Twenty-four hours before surgery I always prescribe a broad-spectrum antibiotic; this may not be necessary, but none of my patients ever has developed a contaminated wound that could be attributed to the gastroenteroscopy.

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6. ESOPHAGITIS: Report of a Case Treated Surgically. Roy H. Thompson, M.D., Cleveland, Ohio.

A 65-year-old housewife was admitted to Woman's Hospital on August 8, 1953, because of complaints of heartburn, nausea, and progressively severe postprandial emesia for the preceding three months. The physical examination was essentially negative. Roentgenographic studies revealed a moderately dilated esophagus with esophagitis, cholecystitis, and cholelithiasis. After discharge from the hospital 15 days after admission, the referring surgeon performed several esophageal dilatations.

Three months after initial admission, the patient was readmitted because of dysphagia and emesia. Through a left thoracotomy, the diaphragm was opened and sutured loosely about the esophagus. She was discharged 25 days postoperatively.

Eleven months after initial admission the patient was readmitted to the hospital. In spite of continued dilatations, her symptoms had worsened and she steadily had lost weight. The thoracotomy was reopened and the junction of the esophagus and stomach

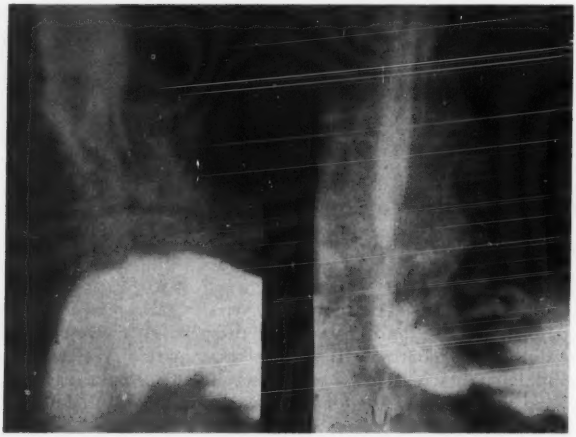
was resected. A new stoma was made in the cardia anteriorly, into which the esophagus was inserted with a long stump and invaginated. The diaphragm was loosely closed around the cardia that remained partly in the thorax.

The pathologic specimen was 4 cm. in length and 1.75 to 3 cm. in diameter. Histopathologic study showed chronic esophagitis and gastritis with stenosis of the esophageal lumen.

The patient's weight decreased to 80 pounds and esophageal dilatation was resumed under fluoroscopic control. Gradually the ability to swallow liquids was regained. The patient's diet progressively included increasingly solid foods. When therapy had reached a degree sufficient to allow the passage of a No. 45 F. olive-tipped bougie, the patient was discharged—approximately three months after admission.

The patient first noted heartburn, a symptom of regurgitation, three months prior to her initial hospitalization. Experimentally, Giuseffi, Grindlay, and Schmidt (Giuseffi, V. G., Jr., Grindlay, J. H., and Schmidt, H. W.: Proc. Staff Meet., Mayo Clin. **29**: 399, 1954) found that esophagitis developed in dogs approximately three months after the removal of the phrenic crura that controls canine regurgitation. Schmidt also reported a large series of cardiospasm patients, one third of whom had disease of the gall bladder (Schmidt, H. W.: Proc. Staff Meet., Mayo Clin. **29**: 153, 1954). Furthermore, the actions of the myenteric plexus of Auerbach and of the submucosal plexus of Meissner are correlated and account for the powerful circular muscles secondary to the inflammation in the wall of the lower esophagus in esophagitis. In the case of this report the first operation removed the effect of the diaphragm with no improvement. The second operation eliminated the normal gastric opening and removed the diseased area.

At follow-up examination two years postoperatively (Fig.), the new stoma functioned normally with no evidence of regurgitation in the upright and in the Trendelenburg positions. The patient had gained 55 pounds and had no complaints.



Roentgenograms after barium swallow, obtained two years postoperatively: (a) No regurgitation apparent (patient in 45-degree Trendelenburg position); (b) Patent stoma (patient in upright position).

This operation is not new and has been reported as attended with varying degrees of success.

In conclusion, it may be said that the pinchcock action of diaphragm and the cardiac and inferior esophageal sphincters do not appear to be essential to prevent abnormal regurgitation.

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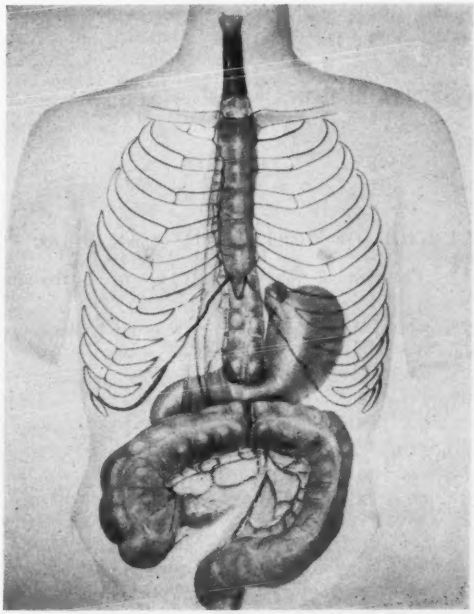
7. ESOPHAGEAL RECONSTRUCTION UTILIZING THE TRANSVERSE COLON.

William E. Neville, M.D., Cleveland, Ohio.

Recent interest in the utilization of the transverse colon in esophageal reconstruction has resulted from consideration of the three great advantages offered by this method: (1) excellent blood supply; (2) bowel length usually adequate to reach the neck in the case of the high esophageal resection; and (3) greater inherent resistance of the colon to peptic ulceration than that either of the jejunum or of the stomach, each of which has been used in esophageal reconstruction.

This report outlines my experience in utilizing the transverse colon for esophageal reconstruction after resection for carcinoma or tracheo-esophageal fistula (Fig.).



Schematic drawing showing the result of utilizing the transverse colon for esophageal reconstruction after operation for tracheo-esophageal fistula.

Two teams of surgeons and assistants have been employed for resection of an esophageal carcinoma above the aortic arch. The 'thoracic' team resects the esophageal lesion through a right thoracotomy, while the 'abdominal' team mobilizes the colon. Either the proximal or the distal end of the bowel is passed into the chest through an incision in the diaphragm anterior to the liver. The thoracic team performs the high esophageal anastomosis either anterior or posterior to the hilum, while simultaneously the abdominal team performs the colocolostomy and cologastrostomy. For esophageal lesions below the aortic arch, the entire operation can be performed through a left transthoracic transdiaphragmatic incision. We have performed this operation on nine patients with carcinoma, with satisfactory results to date.

Delayed reconstruction of the esophagus using the transverse colon has been performed on one child with tracheo-esophageal fistula. Immediately after ligation of the fistula, it was impossible primarily to anastomose the ends of the esophagus; therefore, the blind upper end of the esophagus was brought out into the neck, and the atretic lower end was resected. A feeding gastrostomy was performed through a separate abdominal incision. When the child was one year old, the transverse colon was interposed between the upper end of the esophagus and the stomach. In this instance, the colon was passed into the neck through an anterior mediastinal tunnel. One end was anastomosed to the esophagus, and the other to the distal end of the stomach. Except for requiring subsequent revision of the esophagocolostomy, the patient has progressed well. He eats in a normal manner and his weight has steadily increased.

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8. INTERBODY SPINAL FUSIONS. J. R. Stacy, M.D., Oklahoma City, Oklahoma.

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9. TRANSPLANTATION OF URETERS INTO AN ILEAL POUCH. James I. Farrell, M.D., and John E. Kearns, M.D., Evanston, Illinois.

Diversion of the urinary stream, after cystectomy for carcinoma or because of congenital anomaly, generally has been unsatisfactory. Various operations that have been devised to divert the urinary stream into the colon have had mortality rates up to 50 per cent, and the survivors often have had serious sequelae, including hyperchloremic acidosis, colon-ureteral reflux, renal damage, and stricture at the site of anastomosis.

Recently Hoeffner and Bricker reported good results after transplantation of ureters into isolated segments of ileum, without the late complications of urinary infection and acidosis. We have been favorably impressed with the principle of their procedure for several reasons: (1) the site of implantation remains free of infection; (2) there is no pressure exerted on the transplanted ureter to cause stasis; (3) there is no absorption of urinary waste products from the ileal pouch; (4) since no attempt is made to reconstruct a sphincter between the intestine and the ureter, there is little likelihood of stricture. We have used this procedure in six patients with carcinoma of the bladder. Short-term results have been good.

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10. LIPOMATOUS REPLACEMENT OF THE KIDNEY: Report of Two Cases.

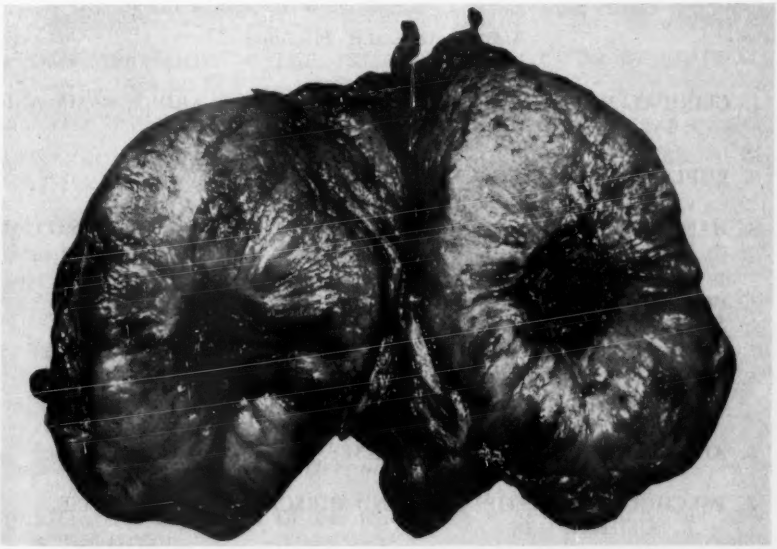
Richard C. Crowell, M.D., St. Joseph, Michigan.

Lipomatous replacement of the kidney, although uncommon, must be considered in the differential diagnosis between renal tumor and renal stone, with or without pyonephrosis.

It is described by Bell (Bell, E. T.: Renal Diseases. Philadelphia, Lea & Febiger, ed. 5, 1946) under the term *lipomatosis*, as a benign disease that rarely causes symptoms other than those attributable to associated renal calculi or pyonephrosis, unless the growth becomes very large.

Since the term *lipomatosis* implies the presence of lipomas, which may become the site of sarcomatous change, the term *lipomatous replacement* better characterizes the process. The fat that replaces the renal parenchyma in this condition arises from the peripelvic fat or from the fat in the renal sinus; the stimulus to its growth is believed to be atrophy of renal tissue. This atrophy is attributable to renal calculi in most cases (76 to 79 per cent), to pyelonephritis fibrosis, or less commonly, to renal tuberculosis. The fatty overgrowth merely replaces lost renal tissue and is not invasive, so that only exceptionally does it become massive and present as a tumor.

Preoperative differential diagnosis is difficult, particularly in the absence of renal stone. The kidney is usually functionless, and pyelography shows deformities that cannot be distinguished from those of renal pelvic or parenchymal tumor. This difficulty is illustrated in the two cases presented. The first patient had a long history of left renal calculus and was considered to have a calculous pyelonephrosis. The initial findings in the second patient strongly suggested either renal neoplasm or nonopaque calculi. The indicated treatment in both patients was nephrectomy—more urgently in the second because of the possibility of renal tumor.



Cross section of the gross specimen of the kidney of the second patient, showing inspissated old blood and pus in the pelvis of the kidney and only a fine rim of renal tissue remaining.

Saturday, September 10

Morning Sessions

R. S. Dinsmore, M.D., *Presiding*

1. GRAFTING FOR MAJOR ARTERIAL OCCLUSIONS. A. W. Humphries, M.D.
2. CARDIOVASCULAR RESEARCH. I. H. Page, M.D.
3. SELECTION OF PATIENTS FOR SURGERY FOR CARDIAC LESIONS. A. C. Ernstene, M.D.

A. C. Ernstene, M.D., *Presiding*

1. CLINICAL USE OF TAPE RECORDED ELECTROCARDIOGRAMS AND HEART SOUNDS. W. L. Proudfit, M.D.
2. LUPUS ERYTHEMATOSUS. J. R. Haserick, M.D.
3. HAMANN-RICH SYNDROME (CHRONIC FIBROSING INTERSTITIAL PNEUMONITIS). H. S. Van Ordstrand, M.D.
4. PRIMARY ALDOSTERONISM: PRESENTATION OF CASE. E. P. McCullagh, M.D.
5. AMEBIASIS: THE USE OF NEWER DRUGS IN TREATMENT. C. H. Brown, M.D.
6. ABNORMAL HEMOGLOBIN DISEASES. J. S. Hewlett, M.D.
7. PSYCHOGENIC OBSTIPATION AND HIRSCHSPRUNG'S DISEASE. R. D. Mercer, M.D.
8. CARDIAC CATHETERIZATION. F. M. Sones, Jr., M.D.

Present Policies in the Treatment of Cancer

George Crile, Jr., M.D., *Presiding*

1. BREAST. R. S. Dinsmore, M.D.
2. HEAD AND NECK. Robin Anderson, M.D.
3. LARYNX. H. E. Harris, M.D.
4. THYROID. J. B. Hazard, M.D.
5. ESOPHAGUS. L. K. Groves, M.D.
6. LUNGS. D. B. Effler, M.D.
7. STOMACH. S. O. Hoerr, M.D.
8. COLON. R. B. Turnbull, Jr., M.D.
9. BLADDER. W. J. Engel, M.D.
10. UTERUS AND CERVIX. J. S. Krieger, M.D.
11. COBALT 60. C. M. Greenwald, M.D.
12. BONE SARCOMA. G. S. Phalen, M.D.

DISCUSSION

1. DECOMPRESSION OF THE TRIGEMINAL ROOT FOR TRIGEMINAL NEURALGIA. K. P. Taarnhøj, M.D.
2. PHEOCHROMOCYTOMA. E. F. Poutasse, M.D.
3. SURGICAL POLICY IN TREATMENT OF DUODENAL ULCER. S. O. Hoerr, M.D.
4. A NEW TYPE OF ILEOSTOMY (Movie). R. B. Turnbull, Jr., M.D.
5. THE X-RAY IN DIAGNOSIS OF INTESTINAL OBSTRUCTION. C. R. Hughes, M.D.
6. SPECIALIZED DENTAL SERVICE TO CHILDREN. J. K. Dunn, D.D.S.
7. TREATMENT OF OPTIC NEURITIS WITH ACTH AND TYPHOID VACCINE. R. J. Kennedy, M.D.

Afternoon Program

UNVEILING OF PORTRAIT OF DR. HADEN. W. E. Flannery, M.D., and John Tucker, M.D.

NEW HOSPITAL—REMARKS. R. S. Dinsmore, M.D.